ENVIRONMENTAL TOBACCO SMOKE

EXPOSURE STUDIES

A REVIEW OF THE LITERATURE

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023379843

2023379844

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023379845

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

ETS: A CHARACTERIZATION

- Environmental tobacco smoke (ETS) is an aged and dilute mixture of sidestream smoke (SS), or the smoke from the burning end of the cigarette, and exhaled mainstream smoke (MS), the smoke to which the smoker is exposed.

- ETS differs chemically and physically from both MS and SS. ETS is a dynamic, ever-changing mixture which, as it ages and dissipates, undergoes chemical reactions and physical change. There is no single definable, reproducibly characterizable entity known as ETS.

- Dissipative forces such as air currents and attraction to surfaces influence SS and exhaled MS. Studies indicate that constituents in ETS are hundreds to thousands of times more dilute than either SS or MS. Often, concentrations of ETS constituents fall below detection limits of current scientific measurement devices.

- As ETS ages, a number of physico-chemical changes take place. Matter evaporates from SS particles as they age to ETS. During the aging process, ETS particles coagulate and increase in size. Chemical compounds partition between the gas and

2023379846

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

particle phase of the smoke. (For example, nicotine is found in the particle phase of MS; in fresh SS, most of the nicotine is in the gas phase.) Decay patterns for constituents of ETS vary over time and are dependent upon physical conditions in the environment.

- ETS is not equivalent to either MS or SS. Many studies and reviews employ sidestream/mainstream smoke comparisons, ostensibly to demonstrate the kind and quantity of constituents involved in exposure to ETS. But such comparisons are deceptive and misleading. As two tobacco smoke chemists reported in 1990:[1]

> Although ETS originates from sidestream and exhaled mainstream smoke, the great dilution and other changes which these smoke streams undergo as they form ETS make their properties significantly different from those of ETS. Thus, the sidestream/mainstream ratios quoted in Table 1 can be misleading if used out of context. The important question is not the ratio of sidestream/mainstream but rather what is the concentration of the constituent in the indoor environment and how does it compare to levels from sources other than ETS. Studies based solely on observations of fresh sidestream, or highly and unrealistically concentrated ETS, should take into account the possible differences between these smokes and ETS found in real-life situations.

2023329847

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

- Even the 1986 Report of the Surgeon General on ETS and the 1986 NRC/NAS Report on ETS conceded:

> Comparison of the relative concentrations of various components of SS and MS smoke provides limited insights concerning the toxicological potential of ETS in comparison with active smoking. As described above, SS characteristics, as measured in a chamber, do not represent those of ETS, as inhaled by the non-smoker under nonexperimental conditions.[2]

Similarly, the NAS Report concluded:

> Because the physicochemical nature of ETS, MS, and SS differ, the extrapolation of health effects from studies of MS or of active smokers to nonsmokers exposed to ETS may not be appropriate . . . .[3]

2023379848

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Baker, R. and C. Proctor, "The Origins and Properties of Environmental Tobacco Smoke," Env. Int. (16): 231-245, 1990.

See also:

Löfroth, G., et al., "Characterization of Environmental Tobacco Smoke," Env Sci Technol (23): 610-614, 1989.

Scherer, G., et al., "Importance of Exposure to Gaseous and Particulate Phase Components of Tobacco Smoke in Active and Passive Smokers," Occup. Env. Health (62): 459-466, 1990.

Nystrom, C., et al., "Assessing the Impact of Environmental Tobacco Smoke on Indoor Air Quality: Current Status," Proceedings of the ASHRAE Conference, IAQ '86, April 20-23, 1986, Atlanta, Georgia: 213-233, 1986.

Rawbone, R., "The Aging of Sidestream Tobacco Smoke Components in Ambient Environments," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 55-61, 1990.

Proctor, C. and H. Dymond, "The Measurement of ETS Through Adsorption/Desorption Procedures," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 82-89, 1990.

Piade, J., et al., "Assessment of ETS Impact on Office Air Quality," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 112-119, 1990.

2. U.S. Department of Health and Human Services, A Report of the Surgeon General, The Health Consequences of Involuntary Smoking: 23-25, 1986.

3. Committee on Passive Smoking, Board on Environmental Studies and Toxicology, National Research Council, Environmental Tobacco Smoke, Measuring Exposures and Assessing Health Effects, National Academy Press, Washington, D.C.: 7-9, 1986.

2023379849

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023379850

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

EXPOSURE TO ETS

- Published studies indicate that nonsmoker exposure to ETS under normal, everyday conditions is minimal. For example, researchers report that there is little difference in ambient levels of carbon monoxide in smoking and nonsmoking areas of workplaces and public places and in homes with and without smokers.[1-6] Other studies indicate that ETS contributes less than half of the total particles in the air of a typical public place.*[7-14] Nicotine is often used as a marker for ETS

---

* A paper published in a 1980 issue of Science magazine, in which the authors reported the results of their efforts to measure particles or particulates in the air of smoking and nonsmoking areas, is often cited to support the claim that ETS is a major indoor pollutant. The authors, Repace and Lowrey, contend that the levels of particles they observed in the smoking areas were much higher than in the nonsmoking areas. However, their study results are inconsistent with many others. For example, the average particle count attributed to ETS in their study was from three to twenty times higher than the average levels reported in other studies of office buildings, restaurants and residences.

There are a number of explanations for the authors' apparent overestimation of ETS exposure. First, they selectively sampled environments such as meeting and game rooms, bars and sandwich shops which did not represent normal occupancy conditions and where particulate levels would likely be high regardless of the presence or absence of tobacco smoke. Second, through inappropriate testing methods, they incorrectly assumed all particles in the air arose from ETS. However, as several researchers have noted, ETS typically contributes about one-third of the overall particle levels in indoor spaces. Moreover, particles also are generated by people and their everyday routine activities such as movement and cooking. (Repace, J. and A. Lowrey, "Indoor Air Pollution, Tobacco Smoke and Public Health," Science 208: 464-472, 1980.)

2023279851

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

exposures because it is unique to tobacco smoke. Typical measurements of nicotine range from an exposure equivalent of 1/100 to 1/1000 of one filter cigarette per hour.[15-22] This means that a nonsmoker would have to spend from 100 to 1000 hours in an office, restaurant or public place in order to be exposed to the nicotine equivalent of a single cigarette.

- Studies which have examined ETS constituent levels of nitrosamines, nitrogen oxides and volatile organic compounds (such as benzene**) report minimal contributions to overall ambient air levels in homes, the workplace and public places.[23-36]

** Benzene exposure from ETS is negligible, despite reports to the contrary.[37-38] "Automotive fuel is, by far, the largest, most pervasive source of benzene exposure. In 1989, the U.S. Department of Health and Human Services estimated that 1 billion pounds of benzene were released into the atmosphere from the refueling and operation of approximately 130 million motor vehicles in 1976 [NIEHS, 1989]. This translates into 7.8 pounds of benzene per vehicle per year. In contrast, a pack-per-day smoker would generate approximately 0.008 pounds of benzene per year, assuming that, at most, 0.5 mg of benzene is generated from one cigarette (MS plus SS) [Hoffmann, 1990]. Based on these estimates, an average person is potentially exposed to 1,000 times more ambient benzene from one automobile than from a smoker in a given year." [From: Response of RJR, The U.S. EPA: "ETS: A Guide to Workplace Smoking Policies," October 1, 1990.]

2023379852

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Questionnaire Reliability:

- All of the epidemiologic studies on the purported association between ETS exposure and disease in nonsmokers rely solely upon questionnaires about exposure, rather than upon actual exposure data.[39-41] Recent studies indicate that questionnaires are an unreliable and inaccurate measure of exposure. Questionnaire responses about exposure vary widely when compared with actual measurements of ETS constituents in the ambient air.[41]

ETS and Radon:

- A theory that suggests that concentrations of radon decay products increase in the presence of tobacco smoke, thus implying an increased risk of lung cancer for the nonsmoker, has been reported in the literature.[42-44] The theory suggests that radon decay products attach to particles (including ETS) in the air, remain suspended, and are subsequently taken up in the lungs of nonsmokers.

- However, actual data indicate that this is not the case.[45-48] It is the unattached, gaseous fraction of radon which determines the dose of radiation to the respiratory tract. According to these data, as dust or particulate levels

2023379853

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

increase, the unattached fraction of radon daughters will decrease, thereby lowering the potential dose of radiation to the lungs.

2023379854

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Kirk, P., et al., "Environmental Tobacco Smoke in Indoor Air," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk, London, Selper Ltd.: 99-112, 1988.

2. Duncan, D. and P. Greavey, "Passive Smoking and Uptake of Carbon Monoxide in Flight Attendants," JAMA 251(20): 120-21, 1984.

3. Cox, B. and M. Whichelow, "Carbon Monoxide Levels in the Breath of Smokers and Nonsmokers: Effect of Domestic Heating Systems," J Epidemiol Community Health 39: 75-78, 1985.

4. Girman, J. and G. Traynor, "Indoor Concentrations," J Am Pollut Control Assoc 33(2): 89, 1983.

5. Yocom, J., "Indoor Concentrations," JAPCA, 33(2): 89, 1983.

6. Nitta, H., et al., "Measurements of Indoor Carbon Monoxide Levels Using Passive Samplers in Korea," Indoor Air '90: The Fifth International Conference on Indoor Air Quality and Climate, Toronto, Canada, July 29-August 3: 77-82, 1990.

7. Carson, J. and C. Erikson, "Results from Survey of Environmental Tobacco Smoke in Offices in Ottawa, Ontario," Environ Technol Letters 9: 501-508, 1988.

8. Sterling, T., et al., "Environmental Tobacco Smoke and Indoor Air Quality in Modern Office Work Environments," J. Occup. Med. 26(1): 57-62, 1987.

9. Sterling T. and B. Mueller, "Concentrations of Nicotine, RSP, CO and CO_2 in Nonsmoking Areas of Offices Ventilated by Air Recirculated From Smoking Designated Areas," Am. Ind. Hyg. Assoc. J., 49(9): 423-426, 1988.

10. Hosein, R., "The Relationship Between Pollutant Levels in Homes and Potential Sources;" Indoor Air Quality in Cold Climates, Hazards and Abatement Measures, ed. D. Walkinshaw, Ottawa, Ontario, APCA: 250-260, 1985.

11. Proctor, C., et al., "Measurements of Environmental Tobacco Smoke in an Air-Conditioned Office Building," Environ. Technol. Letters (10): 1003-1018, 1989.

2023379855

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

12. Oldaker, G., et al., "Results From Surveys of Environmental Tobacco Smoke in Restaurants," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 99-104, 1990.

13. Spengler, J., "Harvard's Indoor Air Pollution Health Study," Indoor Air Quality, H. Kasuga (ed.), Springer-Verlag, Berlin Heidelberg: 241-248, 1990.

14. Quackenboss, J. and Lebowitz, M., "Indoor-Outdoor Relationships for Particulate Matter: Exposure Classifications and Health Effects," Environ. Int., 15: 353-360, 1989.

15. Hinds, W. and First, M., "Concentrations of Nicotine and Tobacco Smoke in Public Places," New Eng. J. Med. 292(16): 844-845, 1975.

16. Badre, R., et al., "Pollution Atmospherique par la Fumee de Tabac (Atmospheric Pollution by Smoking)," Ann. Pharm. Fr. 36(9-10): 443-452, 1978. Translation.

17. Jenkins, R., et al., "Development and Application of a Thermal Desorption-Based Method for the Determination of Nicotine in Indoor Environments," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk, London, Selper Ltd.: 557-566, 1988.

18. Muramatsu, M., et al., "Estimation of Personal Exposure to Tobacco Smoke with a Newly Developed Nicotine Personal Monitor," Environ. Res. 35: 218-227, 1984.

19. Muramatsu, M., et al., "Estimation of Personal Exposure to Ambient Nicotine in Daily Environment," Arch. Occup. Environ. Health 59: 545-550, 1987.

20. Thompson, C., et al., "A Thermal Desorption Method for the Determination of Nicotine in Indoor Environments," Envir. Sci. Tech. 23: 429-435, 1989.

21. Foliart, D., et al., "Passive Absorption of Nicotine in Airline Flight Attendants," New Eng. J. Med., 308(18): 1105, 1983.

22. Oldaker, G. and Conrad, F., "Estimation of the Effect of Environmental Tobacco Smoke on Air Quality Within Passenger Cabins of Commercial Aircraft," Envir. Sci. Tech. 21: 994-999, 1987.

23. Lehnert, G., "Conclusion: In the Realm of Speculation," Munch med Wschr, 124 (1982) Nr. 4.

2023379856

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

24. Schievelbein, H., "Are There Really Important New Findings About Passive Smoking?," Oeff Gesundheitswes, 44(0): 454-56, 1982. Translation.

25. Stehlik, G., et al., "Concentration of Dimethylnitrosamine in the Air of Smoke-Filled Rooms," Ecotoxicol Environ Safety 6: 495-500, 1982.

26. Sega, K. and M. Fugas, "Nitrogen Dioxide Concentrations in Residences," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk, London, Selper Ltd.: 493-496, 1988.

27. Good, B., et al., "Effect of Cigarette Smoking on Residential NO_2 Levels," Environ Int 8: 167-175, 1982.

28. Shimizu, Y., et al., "Influence of Indoor Air Pollution on NO_2 Personal Exposure Levels of Schoolchildren," Present and Future of Indoor Air Quality, eds. C. Bieva, et al., Brussels, Elsevier: 337-345, 1989.

29. Hendel-Kramer, A., et al., "Regression Model for Indoor Concentrations of Combustion-Generated Gases," Present and Future of Indoor Air Quality, eds. C. Bieva, et al., Brussels, Elsevier: 315-320, 1989.

30. Bayer, C. and Black, M., "Thermal Desorption/Gas Chromatographic/Mass spectrometric Analysis of Volatile Organic Compounds in the Offices of Smokers and Nonsmokers," Biomed and Envir Mass Spect 14(8): 363-367, 1987.

31. Proctor, C., et al., "Measurements of Environmental Tobacco Smoke in an Air-Conditioned Office Building," Environ. Technol. Letters (10): 1003-1018, 1989.

32. Godish, T., "Formaldehyde Exposures from Tobacco Smoke: A Review," AJPH 79(8): 1044-1045, 1989.

33. Godish, T., "Residential Formaldehyde: Increased Exposure Levels Aggravate Adverse Health Effects," J. of Environ. Health 53(3): 34-35, 1990.

34. Adlkofer, F., et al., "Significance of Exposure to Benzene and Other Toxic Compounds Through Environmental Tobacco Smoke," J. Cancer Res. Clin. Oncol. (116): 591-598, 1990.

35. Hugod, C., et al., "Exposure of Passive Smokers to Tobacco Smoke Constituents," Int. Arch. Occup. Environ. Health (42): 21-29, 1978.

2023279857

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

36. Proctor, C., et al., "Measurement of Environmental Tobacco Smoke in an Air-Conditioned Office Building," Present and Future of Indoor Air Quality, eds. C.J. Bieva, et al., Brussels, Elsevier: 169-172, 1989.

37. Hattemer-Frey, H., "Benzene: Environmental Partitioning and Human Exposure," Environ. Res., 53: 221-232, 1990.

38. Wallace, L., "Major Sources of Exposure to Benzene and Other Volatile Organic Chemicals," Risk Analysis, 10(1): 59-64, 1990.

39. Coultas, D., et al., "Questionnaire Assessment of Lifetime and Recent Exposure to Environmental Tobacco Smoke," Am J of Epi. 130(2): 338-347, 1989.

40. Coultas, D., et al., "Variability of Measures of Exposure to Environmental Tobacco Smoke in the Home," Am Rev Resp Dis 142: 602-606, 1990.

41. Coultas, D., et al., "A Personal Monitoring Study to Assess Workplace Exposure to Environmental Tobacco Smoke," American J. of Public Health 80(8): 988-990, 1990.

42. Bergman, H. and Axelson, O., "Passive Smoking and Indoor Radon Daughter Concentrations," Lancet: 1308-09, 1983.

43. Bergman, H., et al., "Indoor Radon Daughter Concentrations and Passive Smoking," Env. Int. (12): 17-19, 1986.

44. Moghissi, A. and M. Seiler, "Enhancement of Exposure to Radon Progeny as a Consequence of Passive Smoking," Env. Int. (15): 261-64, 1989.

45. Upfal, M., et al., "Indoor Radon and Lung Cancer in China," J. Nat. Cancer Inst.: 1722, 1989.

46. Stebbings, J. and J. Dignam, "Contamination of Individuals by Radon Daughters: A Preliminary Study," Archives of Environ. Health 43(2): 149-54, 1988.

47. Pritchard, J. and J. Strong, "The Influence of Environmental Tobacco Smoke on Radon Dosimetery," Indoor Air '90: The Fifth International Conference on Indoor Air Quality and Climate, Toronto, Canada, July/August 1990: 33-38.

48. McAughey, J., et al., "Risk Assessment of Exposure to Indoor Air Pollutants," Env. Int. (11): 295-302, 1990.

2023379858

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023379859

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

DETERMINATION OF DOSE: COTININE

- It has been reported that cotinine, a substance converted from nicotine by the body, can be used as a biological marker to measure nonsmoker exposure to ETS.[1-2] While some reports suggest that cotinine is a reliable marker for total exposure to tobacco smoke, many others do not.[3-12] Researchers have reported that individuals metabolize nicotine in different ways at different times and that elimination rates for cotinine vary among individuals. In addition, recent research indicates that diet may contribute to levels of nicotine and cotinine found in the body, thereby interfering with ambient air exposure levels.[13] Scientists have also noted that different methods of analysis may influence final recorded levels of cotinine.[14] And finally, because cotinine is a metabolite of a gas-phase constituent of ETS, nicotine, cotinine levels do not represent exposures to other constituents of ETS.

- In conclusion, cotinine is not a reliable quantitative measure of ETS exposure. This is because body fluid levels of cotinine cannot be attributed solely to nicotine in ETS, and because body fluid levels of cotinine do not correlate well with actual ambient air exposures to ETS or with ETS constituents other than nicotine. At best, cotinine may be used as a qualitative marker of ambient nicotine exposures.

2023379860

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Wald, N., et al., "Urinary Cotinine as Marker of Breathing Other People's Tobacco Smoke," Lancet I, 230-231, 1984.

2. Watts, R. et al., "Cotinine Analytical Workshop Report: Consideration of Analytical Methods for Determining Cotinine In Human Body Fluids as a Measure of Passive Exposure to Tobacco Smoke," Environ. Health Pers. 84: 173-182, 1990.

3. Curvall, M., et al., "Simulation and Evaluation of Nicotine Intake During Passive Smoking: Cotinine Measurements in Body Fluids of Nonsmokers Given Intravenous Infusions of Nicotine," Clin. Pharmacol. Ther. 47(1): 42-49, 1990.

4. Itani, S., et al., "A Comparison of Plasma and Urinary Nicotine and Cotinine Levels in Smokers and Nonsmokers: Nicotine Excretion Pathways are Possibly Differential According to the Dosage of Tobacco Smoke Uptake," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 202-212, 1990.

5. Idle, J., "Commentary: Titrating Exposure to Tobacco Smoke Using Cotinine -- A Minefield of Misunderstanding," J. Clin. Epidemiol. 43(4): 313-317, 1990.

6. Biber, A., et al., "Determination of Nicotine and Cotinine in Human Serum and Urine: An Interlaboratory Study," Toxicology Letters 35(1): 45-52, 1987.

7. Haley, N. et al., "Elimination of Cotinine from Body Fluids: Disposition in Smokers and Nonsmokers," AJPH 79(8): 1046-1048, 1989.

8. Cummings, K., et al., "Measurement of Current Exposure to Environmental Tobacco Smoke," Archives of Environ. Health 45(2): 74-79, 1990.

9. Lee, P., "Lung Cancer and Passive Smoking," Br. J. Cancer, 63: 161-162, 1991.

10. Johnson, L., et al., "Passive Smoking Under Controlled Conditions," Int. Arch. Occup. Environ. Health 56: 99-110, 1985.

11. Letzel, H., et al., "Measuring Problems in Estimating the Exposure to Passive Smoking Using the Excretion of Cotinine," Toxicology Letters 35(1): 35-44, 1987.

2023279861

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

12. Schwartz, S., et al., "Mathematical Modelling of Nicotine and Cotinine as Biological Markers of Environmental Tobacco Smoke Exposure," Toxicology Letters 35(1): 53-58, 1987.

13. Castro, A. and N. Monji, "Dietary Nicotine and Its Significance in Studies on Tobacco Smoking," Bio Arch 2(2): 9197, 1986.

14. Adlkofer, F., et al., "Passive Smoking," N Engl J Med 312(11): 719-720, 1984.

2023379862

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

DETERMINATION OF DOSE: LUNG RETENTION

- Cotinine is a biologically inactive substance which has not been correlated with ETS constituents retained in the lung. Several researchers have estimated levels of ETS particulate uptake by nonsmokers to approximate 0.02% (two-hundredth of one percent) that of the particulate exposure of an active smoker.[1-4]

2023379863

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Arundel, A., et al., "Never Smoker Lung Cancer Risks from Exposure to Particulate Tobacco Smoke," Environ Int 13: 409-426, 1987.

2. Adlkofer, F., "Biological Effects After Exposure to ETS," Indoor Air Quality: Symposium, Buenos Aires, National Academy of Sciences of Buenos Aires: 61-76, 1989.

3. McAughey, J., et al., "Respiratory Deposition of Environmental Tobacco Smoke," Indoor Air '90: The Fifth International Conference on Indoor Air Quality and Climate, Toronto, Canada, July/August: 361-366, 1990.

4. Comments of the R.J. Reynolds Tobacco Company on Appendix C to the EPA Draft Risk Assessment - Dosimetry of Environmental Tobacco Smoke, September 1990, B-1 - C-7.

2023379864

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

DETERMINATION OF DOSE: MUTAGENS

- Some reports have suggested that the potential toxicity of ETS can be assessed by measuring mutagens in the body fluids of nonsmokers exposed to ETS.[1-3] Mutagens are substances capable of altering the genetic structure of cells. It is suggested that the presence of mutagens in body fluids (e.g. urine) may be an indication that an individual has been exposed to substances capable of inducing cancer.

- Impetus for the theory arises, in part, from studies which report that various constituents of ETS collected through airborne samples are capable of inducing mutations in bacteria.[4-6]

- However, the significance of such reported findings has not been established. Virtually all air samples, whether in the presence or absence of smoking, are mutagenic. Indeed, no substance, including food and natural materials, has been unequivocally shown to be free of carcinogenic and/or mutagenic properties. In addition, it has been reported that sidestream smoke exhibits diminished mutagenic activity as it ages and becomes diluted (i.e., as it becomes ETS).[7]

2023379865

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

- With few exceptions, studies which have compared mutagens in the body fluids of nonsmokers exposed to realistic levels of ETS and nonsmokers not exposed to ETS report no significant difference in mutagenic activity.[8-11]

- The few studies reporting significant increases in urinary mutagenicity among individuals exposed to ETS[1-3] did not employ realistic levels of exposure to ETS, and they did not control adequately for the presence of mutagens in the diet of the study subjects.

2023379866

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Bos, R., et al., "Excretion of Mutagens in Human Urine After Passive Smoking," Cancer Letters (19): 85-90, 1983.

2. Husgafvel-Pursiainen, K., et al., "Passive Smoking at Work: Biochemical and Biological Measures of Exposure to Environmental Tobacco Smoke," Int. Arch. Occup. Environ. Health (59): 337-345, 1987.

3. Mohtashamipur, E., et al., "Urinary Excretion of Mutagens in Passive Smokers," Toxicol. Letters (35): 141-146, 1987.

4. Claxton, L., et al., "A Genotoxic Assessment of Environmental Tobacco Smoke Using Bacterial Bioassays," Mutation Res. (222): 81-99, 1989.

5. Lofroth, G., et al., "Public Exposure to Environmental Tobacco Smoke," Mutation Res. (202): 103-110, 1988.

6. Matsushita, H., et al., "Highly Sensitive Methods for the Evaluation of Carcinogens and Mutagens Indoor," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 371-382, 1990.

7. Sonnenfeld, G. and D. Wilson, "The Effect of Smoke Age and Dilution on the Cytotoxicity of Sidestream (Passive) Smoke," Toxicol. Letters (35): 89-94, 1987.

8. Scherer, G., et al., "Urinary Mutagenicity After Controlled Exposure to Environmental Tobacco Smoke (ETS)," Toxicology Letters 35(1): 135-140, 1987.

9. Bombick, D., et al., "Assessment of the Biological Activity of Mainstream or Environmental Tobacco Smoke (ETS) Using a Cellular Smoke Exposure Technique," Abstracts of the Twenty-Second Annual Scientific Meeting of the Environmental Mutagen Society, Kissimmee, Florida: April 1991.

10. Scherer, G., "Biomonitoring of Exposure to Potentially Genotoxic Substances from Environmental Tobacco Smoke," Environ. Int. (15): 49-56, 1989.

11. Scherer, G., "Quantitative and Qualitative Differences in Tobacco Smoke Uptake Between Active and Passive Smoking," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk, Selper Ltd., London: 189-194, 1988.

2023379867

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

DOSE: OTHER BIOLOGICAL MARKERS

- It has been suggested that sidestream smoke (and by inference, ETS) contains polycyclic aromatic hydrocarbons (PAH), substances which have been designated as carcinogens by various governmental agencies. However, in a series of papers, German researchers report no significant differences in urinary PAH by-products among nonsmokers exposed to ETS and those not exposed.[1-3] Diet was reported to have a profound influence on PAH by-product formation in all study subjects.

- Japanese scientists have reported that individuals exposed to ETS have increased urinary levels of hydroxyproline (HOP), a substance believed to act as a marker for the breakdown of lung tissue.[4] However, German researchers have reported no increase in HOP excretion among either smokers or nonsmokers exposed to ETS.[5]

- It has recently been suggested that DNA adducts can be utilized as biomarkers to assess exposure (dose) to ETS.[6] (An adduct is a product derived from reactions between chemicals and biological material (such as DNA)). Research, however, does not conclusively support this theory; nonsmokers exposed to ETS do not appear to exhibit increased DNA adduct production.[7] Other studies report no increased chromosomal changes in body

2023379868

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

fluids of nonsmokers exposed to ETS.[8-9]

2023379869

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Scherer, G., et al., "Urinary Mutagenicity, Hydroxy-Phenanthrene, and Thioether Excretion After Exposure to Environmental Tobacco Smoke," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 138-146, 1990.

2. Martin, F., et al., "Urinary Excretion of Hydroxy-Phenanthrenes After Intake of Polycyclic Aromatic Hydrocarbons," Environ. Int. (15): 41-47, 1989.

3. Hoepfner, H., et al., "Hydroxy-Phenanthrenes in the Urine of Non-Smokers and Smokers," Toxicology Letters (35): 67-71, 1987.

4. Kasuga, H., "An Introduction to the Study of Smoking Using Urinary Hydroxyproline," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 37-52, 1990.

5. Adlkofer, F., "The Significance of Urinary Hydroxyproline Excretion in Smokers and Passive Smokers," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 213-218, 1990.

6. Perera, F., et al., "DNA Adducts, Protein Adducts, and Sister Chromatid Exchange in Cigarette Smokers and Nonsmokers," JNCI 79(3): 449-456, 1987.

7. Holz, O., et al., "^{32}P-postlabelling Analysis of DNA Adducts in Monocytes of Smokers and Passive Smokers," Int. Arch. Occup. Environ. Health, 62: 299-303, 1990.

8. Sorsa, M., et al., "Cytogenetic Effects of Tobacco Smoke Exposure Among Involuntary Smokers," Mutation Res. 222(2): 111-116, 1989.

9. Husgafvel-Pursiainen, K., "Sister-Chromatid Exchange and Cell Proliferation in Cultured Lymphocytes of Passively and Actively Smoking Restaurant Personnel," Mutation Res. 190: 211-215, 1987.

2023379870

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023379871

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

BIOLOGICAL PLAUSIBILITY

- The argument for the biological plausibility of the role of ETS in disease causation depends upon the simplistic claim that since mainstream (MS) and sidestream (SS) smoke contain carcinogenic substances, so must ETS. However, this analogy is not proved.

- ETS has never been shown to be carcinogenic in any animal species. Only two animal inhalation experiments investigating ETS and lung cancer have been published. Both studies report no meaningful histopathological differences between animals exposed to ETS and those which were not exposed. In a study conducted by the American Health Foundation,[1-3] the investigators exposed one group of hamsters to mainstream smoke and another group to ETS. Animals exposed to mainstream smoke and ETS lived longer than the sham treated controls. The investigators reported that overall there was no marked increase in tumor incidence in animals exposed to either mainstream smoke or ETS after 18 months of exposure. The second study was a 90-day ETS inhalation study of rats and hamsters.[4] Animals were exposed to ETS concentrations 100 times those concentrations encountered by nonsmokers. These researchers reported no histopathological differences between exposed and control animals. Electron microscopy revealed

2023379872

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

pulmonary changes which could be expected to occur under similar exposure conditions with other substances.

- In addition, recent reviews of the literature on suspected pulmonary carcinogens have indicated that none of the individual constituents in sidestream smoke classified as potentially carcinogenic has been found to induce pulmonary cancer via inhalation in experimental animals.[5-6]

- ETS has not be shown to be mutagenic in any animal or cell culture system when tested at realistic levels of exposure (See Section III).

- These points undermine the credibility of the argument for the biological plausibility of ETS in disease causation.

2023279873

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Haley, N., et al., "Uptake of Sidestream Smoke by Syrian Golden Hamsters," Toxicol. Letters 35 (1987): 83-88.

2. Haley, N., "Sidestream Smoke Uptake By Syrian Golden Hamsters in An Inhalation Bioassay," Indoor Air '87: Proceedings of the 4th International Conference on Indoor Air Quality and Climate, Institute for Water, Soil and Air Hygiene, Berlin: 68-73, 1987.

3. American Health Foundation, "Experimental Tobacco Carcinogenesis," Application for Continuation Grant to Department of Health and Human Services, U.S. Public Health Service, May 1988.

4. Adlkofer, F., et al., "Exposure of Hamsters and Rats to Sidestream Smoke of Cigarettes: Preliminary Results of a 90-Day-Inhalation Study," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk, London, Selper Ltd.: 252-258, 1988.

5. Aviado, D., "Suspected Pulmonary Carcinogens in Environmental Tobacco Smoke," Environ. Tech. Letters, 9: 539-544, 1988.

6. Aviado, D., "Health Effects of 50 Selected Constituents of Environmental Tobacco Smoke," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 383-389, 1990.

2023379874

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

ETS AND
LUNG CANCER IN NONSMOKERS

VOLUME I

2023379875

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023379876

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

20233379877

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

PRIMARY EPIDEMIOLOGIC STUDIES ON ETS AND LUNG CANCER

Introduction

Currently, 29 epidemiologic studies examining lung cancer incidence and spousal smoking have been published.[1-29] Tables 1, 2 and 3 list the United States, Asian and European studies, respectively. For purposes of comparison, the relative risks (point estimates) given in the tables are the overall point estimates for spousal smoking reported in the papers. In some cases, the risk in the table was selected from numerous point estimates presented in the paper, based on different definitions of exposure, breakdown of the sample by histological type, etc.

Brief synopses and copies of the papers associated with these studies follow this introduction, at Tabs 1 to 29, arranged in chronological order. The copies are highlighted in yellow for useful information and in blue for negative statements.

2023379878

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

United States Studies

Ten of these studies on spousal smoking and lung cancer in nonsmokers (one cohort, nine case-control) were conducted in the United States (Table 1).[3,5,7-9,11,14,16,24,25] **None of the relative risks (RR) for spousal smoking reported in these studies is statistically significant.** The most recently published paper, that by Janerich, et al., is based upon an unpublished dissertation by Luis Varela.[24] The Janerich, et al., paper discusses a subset of Varela's case-control study, and reports no statistically significant increased risk for spousal smoking, workplace exposure, or exposure in social settings. (It does, however, report a statistically significant increased risk for exposure during childhood (see below).) Overall, the Varela study is important because of its large size and appropriate study design.

2023379879

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Table 1. United States Studies of Spousal Smoking in Women

Study	Risk Estimate(s)	Comment
Garfinkel, 1981	1.27 (95% CI 0.85-1.89) 1.10 (95% CI 0.77-1.61)	Large cohort study; results contrast with Hirayama
Correa, et al., 1983	2.07 (no CI; n.s.)	Extremely small sample size
Buffler, et al., 1984	0.78 (95% CI 0.34-1.81)	
Kabat and Wynder, 1984	not given	No significant differences between cases and controls regarding ETS exposure at home
Garfinkel, et al., 1985	1.23 (95% CI 0.94-1.60)	Numerous odds ratios presented
Wu, et al., 1985	1.2 (95% CI 0.5-3.3)	Adenocarcinoma only
Brownson, et al., 1987	1.68 (95% CI 0.39-2.97)	Hours per day as exposure category; adenocarcinoma only
Humble, et al., 1987	1.8 (95% CI 0.6-5.4)	
Varela, 1987	numerous	No statistically significant point estimate was presented in 73 different measures of spousal smoking
Janerich, et al., 1990	0.93 (95% CI 0.55-1.57)	Published data for subset of Varela, 1987
Kabat, 1990	0.90 (95% CI 0.46-1.76)	Study in progress; surrogate is "exposed in adulthood at home"

2023379880

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Asian Studies

In contrast, 13 epidemiologic studies on spousal smoking and lung cancer in nonsmokers (one cohort, twelve case-control) have been conducted in China and Japan (hereafter, "Asian studies") (Table 2).[1,4,10,12,15,17,18,20-22,27,28,29] Of this group, several studies report statistically significant relative risks. However, none of the reported relative risks is greater than 2.5; relative risks under 3.0 have been described as "weak" (see Criticisms section in this notebook). Of particular interest is the 1990 paper by Wu-Williams, et al., conducted in northeastern China.[28] This paper reports a statistically significant negative risk associated with ETS exposure. Other factors (particularly indoor air quality) were reported to be associated with an elevated risk of lung cancer in the Wu-Williams, et al., study; such confounders were not always accounted for in the other Asian studies (see section on Confounders in this notebook).

2023379881

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Table 2. Asian Studies of Spousal Smoking in Women

Study	Point Estimate(s)	Comment
Hirayama, 1981	2.08 (no CI)	Large cohort study; heavily criticized for improper age-standardization and other flaws
Hirayama, 1984	1.45 (90% CI 1.04-2.02)	Further report on above study
Chan and Fung, 1982	not given	Negative association; suggests more "passive smokers" among controls than cases
Lam, W.K., 1985	not given	Unpublished dissertation; suggests that spousal smoking may be associated with peripheral adenocarcinoma
Akiba, et al., 1986	1.5 (90% CI 1.0-2.5)	Study of atom bomb survivors
Gao, et al., 1987	0.9 (95% CI 0.6-1.4)	"Overall exposure" as surrogate
Koo, et al., 1987	1.64 (95% CI 0.87-3.09)	
Lam, T.H., et al., 1987	1.65 (95% CI 1.16-2.35)	
Geng, et al., 1988	2.16 (95% CI 1.03-4.53)	
Inoue and Hirayama, 1988	2.25 (95% CI 0.91-7.10)	Very small sample size
Shimizu, et al., 1988	1.1 (no CI; n.s.)	Reported statistically significant elevated risks for smoking by case's mother or case's husband's father

2023379882

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Study	Point Estimate(s)	Comment
Sobue, et al., 1990	0.94 (95% CI 0.62-1.40)	
Wu-Williams, et al., 1990	0.7 (95% CI 0.6-0.9)	Point estimate is statistically significantly negative
Liu, et al., 1991	0.77 (95% CI 0.30-1.96)	Presence of at least one smoker in household used as surrogate

2023379883

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

European Studies

Six studies on spousal smoking and nonsmoker lung cancer were conducted in Europe (Table 3).[2,7,13,19,23,26] Statistical significance was reported in two studies, both by the same research group.[2,26] No major cohort study has yet been conducted in Europe. The cohort studied by Gillis, et al., and Hole, et al., although large, has few lung cancer deaths.[7]

2023279884

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Table 3. European Studies of Spousal Smoking in Women

Study	Risk Estimate	Comment
Trichopoulos, et al., 1981	2.4 (no CI)	Greece; small case-control study; has been heavily criticized
Trichopoulos, et al., 1983	2.4 (no CI) 3.4 (no CI)	Additional cases and controls added since first paper
Gillis, et al., 1984	not given	Scotland; cohort study; very few lung cancer death (4 cases, 4 controls in women)
Hole, et al., 1989	2.41 (95% CI 0.45-12.83)	Continuation of Gillis, et al., 1984
Lee, et al., 1986	1.00 (95% CI 0.37-2.71)	England
Pershagen, et al., 1987	1.2 (95% CI 0.7-2.1)	Sweden
Svensson, et al., 1989	1.2 (95% CI 0.4-2.9)	Sweden; surrogate is "exposure as adult at home or at work"
Kalandidi, et al., 1990	1.92 (95% CI 1.02-3.59)	Greece; related to Trichopoulos study

2023379885

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Childhood Exposure to ETS and Adult Lung Cancer in Nonsmokers

When the Janerich, et al., paper was published in 1990, the media focused on a single statistically significant risk ratio (OR) reported by the authors, i.e., an estimated OR of 2.07 (95% CI 1.16-3.68) for "household exposure to 25 or more smoker-years during childhood and adolescence."[24] This OR is the only statistically significant estimate out of 13 exposure categories in the paper. A single statistically significant point estimate could have easily occurred by chance alone in a set of analyses this large.

Only a few other studies have included questions concerning exposure to ETS during childhood, i.e., parental smoking.[5,9,11,12,15,23,25,27] Regarding these studies, Ernst Wynder and Geoffrey Kabat wrote in a 1990 publication:

> No consistent association has been reported for lung cancer and exposure to ETS in childhood, which might be expected to exert a greater effect, especially when followed by exposure throughout adulthood. Of course, recall of ETS exposure in childhood is more difficult than recall of such exposure in adulthood.

(Wynder, E.L. and Kabat, G.C., "Environmental Tobacco Smoke and Lung Cancer: A Critical Assessment," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 5-15.)

Table 4 presents the reported risk estimates from the studies (9 to-date) which discuss childhood ETS exposure and lung

2023379886

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

cancer in nonsmokers. The studies are arranged chronologically in the table. The abbreviation "n.s." stands for "not significant."

2023379887

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Table 4. Childhood Exposure to ETS and Adult Nonsmoker Lung Cancer Risk

Study	Point Estimate	Statistical Significance
Correa, et al., 1983	not given	n.s.
Garfinkel, et al., 1985		
females	0.91 (95% CI 0.74-1.12)	n.s.
Wu, et al., 1985		
females	0.6 (95% CI 0.2-1.7)	n.s.
Akiba, et al., 1986	not given	n.s.
Gao, et al., 1987		
females	1.1 (95% CI 0.7-1.7)	n.s.
Svensson, et al., 1989		
females, father's smoking	0.9 (95% CI 0.4-2.3)	n.s.
females, mother's smoking	3.3 (95% CI 0.5-18.8)	n.s.
Janerich, et al., 1990		
1-24 smoker/yrs exposure	1.09 (95% CI 0.68-1.73)	n.s.
≥ 25 smoker/yrs exposure	2.07 (95% CI 1.16-3.68)	significantly positive
Kabat, et al., 1990		
males	0.73 (95% CI 0.34-1.59)	n.s.
females	1.68 (95% CI 0.86-3.27)	n.s.
Sobue, et al., 1990		
father's smoking	0.60 (95% CI 0.40-0.91)	significantly negative
mother's smoking	1.71 (95% CI 0.95-3.10)	n.s.
other household members	1.13 (95% CI 0.69-1.87)	n.s.

2023379888

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Exposure to ETS in the Workplace and Lung Cancer in Nonsmokers

The issue of ETS in the workplace is currently a focus of public interest, as evidenced by the 1990 draft Guide to Workplace Smoking Policies prepared by the United States Environmental Protection Agency. This document is based on the EPA's draft risk assessment, which used data from epidemiologic studies which assessed ETS exposure in terms of spousal smoking, not smoking in the workplace.

The current epidemiologic data on workplace exposures to ETS and lung cancer in nonsmokers are reported in eleven studies which examined workplace exposure via questionnaire.[8,9,11,13,17,22-26,28] None of these studies provides adequate support for an increased risk of lung cancer associated with ETS exposure in the workplace. Only one study reports a single marginally statistically significant risk. The point estimates of the studies (in chronological order) are presented in Table 5. (In the table, "n.s." stands for "not significant.")

2023379889

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Table 5. Exposure to ETS in the Workplace and Lung Cancer Risk in Nonsmokers

Study	Point Estimate	Statistical Significance
Kabat and Wynder, 1984		
males	18/25 cases vs. 11/25 controls	marginally significant
females	26/53 cases vs. 31/53 controls	n.s.
Garfinkel, et al., 1985		
females, 5 yr exposure	0.88 (95% CI 0.66-1.18)	n.s.
females, 25 yr exposure	0.93 (95% CI 0.73-1.18)	n.s.
Wu, et al., 1985		
females	1.3 (95% CI 0.5-3.3)	n.s.
Lee, et al., 1986	several indices	all n.s.
Koo, et al., 1987		
females	several ORs	all n.s.
Shimizu, et al., 1988		
females	1.2 (no CI given)	n.s.
Svensson, et al., 1989		
females, at home or at work	1.2 (95% CI 0.4-2.9)	n.s.
females, at home and at work	2.1 (95% CI 0.6-8.1)	n.s.
Janerich, et al., 1990		
150 person/yrs exposure	0.91 (95% CI 0.80-1.09)	n.s.
Varela, 1987	27 analyses	all n.s.
Kabat, 1990		
males	0.98 (95% CI 0.46-2.10)	n.s.
females	1.00 (95% CI 0.49-2.06)	n.s.

2023379890

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Study	Point Estimate	Statistical Significance
Kalandidi, et al., 1990 females	1.08 (95% CI 0.24-4.87)	n.s.
Wu-Williams, et al., 1990 females	1.1 (95% CI 0.9-1.6)	n.s.

2023379891

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Hirayama, T., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer: A Study from Japan," British Medical Journal I, 282: 183-185, 1981.

   Hirayama, T., "Cancer Mortality in Nonsmoking Women with Smoking Husbands Based on a Large-Scale Cohort Study in Japan," Preventive Medicine 13: 680-690, 1984.

   Hirayama, T., "Lung Cancer in Japan: Effects of Nutrition and Passive Smoking," Lung Cancer: Causes and Prevention, eds. M. Mizell and P. Correa (New York: Verlag Chimie International, 1984): 175-195.

2. Trichopoulos, D., Kalandidi, A., Sparros, L. and MacMahon, B., "Lung Cancer and Passive Smoking," International Journal of Cancer 27(1): 1-4, 1981.

   Trichopoulos, D., Kalandidi, A. and Sparros, L., "Lung Cancer and Passive Smoking: Conclusions of Greek Study," The Lancet II: 677-678, 1983.

3. Garfinkel, L., "Time Trends in Lung Cancer Mortality Among Nonsmokers and a Note on Passive Smoking," Journal of the National Cancer Institute 66: 1061-1066, 1981.

4. Chan, W.C. and Fung, S.C., "Lung Cancer in Non-Smokers in Hong Kong," Cancer Campaign Vol. 6, Cancer Epidemiology, ed. E. Grundmann (Stuttgart: Gustav Fischer Verlag, 1982): 199-202.

5. Correa, P., Pickle, L.W, Fontham, E., Lin, Y. and Haenszel, W., "Passive Smoking and Lung Cancer," The Lancet II: 595-597, 1983.

6. Buffler, P.A., Pickle, L.W., Mason, T.J. and Contant, C., "The Causes of Lung Cancer in Texas," Lung Cancer: Causes and Prevention, eds. M. Mizell and P. Correa (New York: Verlag Chimie International, 1984): 83-99.

7. Gillis, C.R., Hole, D.J., Hawthorne, V.M. and Boyle, P., "The Effect of Environmental Tobacco Smoke in Two Urban Communities in the West of Scotland," ETS - Environmental Tobacco Smoke: Report from a Workshop on Effects and Exposure Levels, eds. R. Rylander, Y. Peterson and M.-C. Snella, European Journal of Respiratory Diseases, Supplement 133(65): 121-126, 1984.

   Hole, D.J., Gillis, C.R., Chopra, C. and Hawthorne, V.M., "Passive Smoking and Cardiorespiratory Health in a General

2023379892

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Population in the West of Scotland," British Medical Journal 299: 423-427.

8. Kabat, G. and E. Wynder, "Lung Cancer in Nonsmokers," Cancer 53: 1214-1221, 1984.

9. Garfinkel, L., Auerbach, O. and Joubert, L., "Involuntary Smoking and Lung Cancer: A Case-Control Study," Journal of the National Cancer Institute 75(3): 463-469, 1985.

10. Lam, W.K., A Clinical and Epidemiological Study of Carcinoma of Lung in Hong Kong, M.D. thesis submitted to University of Hong Kong, 1985 (only some pages available).

11. Wu, A., Henderson, B.E., Pike, M.C. and Yu, M.C., "Smoking and Other Risk Factors for Lung Cancer in Women," Journal of the National Cancer Institute 74(4): 747-751, 1985.

12. Akiba, S., Kato, H. and Blot, W.J., "Passive Smoking and Lung Cancer Among Japanese Women," Cancer Research 46: 4804-4807, 1986.

13. Lee, P., Chamberlain, J. and Alderson, M.R., "Relationship of Passive Smoking to Risk of Lung Cancer and Other Smoking-Associated Diseases," British Journal of Cancer 54: 97-105, 1986.

14. Brownson, R.C., Reif, J.S., Keefe, T.J., Ferguson, S.W. and Pritzl, J.A., "Risk Factors for Adenocarcinoma of the Lung," American Journal of Epidemiology 125(1): 25-34, 1987.

15. Gao, Y.-T., Blot, W.J., Zheng, W., Ershow, A.G., Hsu, C.W., Levin, L.I., Zhang, R. and Fraumeni, J.F., "Lung Cancer Among Chinese Women," International Journal of Cancer 40: 604-609, 1987.

16. Humble, C.G., Samet, J.M. and Pathak, D.R., "Marriage to a Smoker and Lung Cancer Risk," American Journal of Public Health 77(5): 598-602, 1987.

17. Koo, L., Ho, J.H.-C., Saw, D. and Ho, C.-Y., "Measurements of Passive Smoking and Estimates of Lung Cancer Risk Among Non-Smoking Chinese Females," International Journal of Cancer 39: 162-169, 1987.

18. Lam, T.H., Kung, I.T.M., Wong, C.M., Lam, W.K., Kleevens, J.W.L., Saw, D., Hsu, C., Seneviratne, S., Lam, S.Y., Lo, K.K. and Chan, W.C., "Smoking, Passive Smoking and Histological Types in Lung Cancer in Hong Kong Chinese Women," British Journal of Cancer 56(5): 673-678, 1987.

2023379893

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

19. Pershagen, G., Hrubec, Z. and Svensson, C., "Passive Smoking and Lung Cancer in Swedish Women," American Journal of Epidemiology 125(1): 17-24, 1987.

20. Geng, G.-Y., Liang, Z.H., Zhang, A.Y. and Wu, G.L., "On the Relationship Between Smoking and Female Lung Cancer," Smoking and Health 1987, eds. M. Aoki, S. Hisamichi and S. Tominaga (Amsterdam: Excerpta Medica, 1988): 483-486.

21. Inoue, R. and Hirayama, T., "Passive Smoking and Lung Cancer in Women" Smoking and Health 1987, eds. M. Aoki, S. Hisamichi and S. Tominaga (Amsterdam: Excerpta Medica, 1988): 283-285.

22. Shimizu, H., Morishita, M., Mizuno, K., Masuda, T., Ogura, Y., Santo, M., Nishimura, M., Kunishima, K., Karasawa, K., Nishiwaki, K., Yamamoto, M., Hisamichi, S. and Tominaga, S., "A Case-Control Study of Lung Cancer in Nonsmoking Women," Tohoku Journal of Experimental Medicine 154: 389-397, 1988.

23. Svensson, C., Pershagen, G. and Klominek, J., "Smoking and Passive Smoking in Relation to Lung Cancer in Women," Acta Oncologica 28(5): 623-629, 1989.

24. Janerich, D., Thompson, W.D., Varela, L.R., Greenwald, P., Chorost, S., Tucci, C., Zaman, M.B., Melamed, M.R., Kiely, M. and McKneally, M.F., "Lung Cancer and Exposure to Tobacco Smoke in the Household," The New England Journal of Medicine 323: 632-636, 1990.

Varela, L., "Assessment of the Association Between Passive Smoking and Lung Cancer," dissertation submitted to Yale University, 1987.

25. Kabat, G.C., "Epidemiologic Studies of the Relationship Between Passive Smoking and Lung Cancer," Toxicology Forum, 1990 Annual Winter Meeting (transcript): 187-199, 1990.

26. Kalandidi, A., Katsouyanni, K., Voropoulou, N., Bastas, G., Saracci, R. and Trichopoulos, D., "Passive Smoking and Diet in the Etiology of Lung Cancer Among Non-Smokers," Cancer Causes and Control 1: 15-21, 1990.

27. Sobue, T., Suzuki, R., Nakayama, N., Inubuse, C., Matsuda, M., Doi, O., Mori, T., Furuse, K., Fukuoka, M., Yasumitsu, T., Kuwabara, O., Ichigaya, M., Kurata, M., Kuwabara, M., Nakahara, K., Endo, S. and Hattori, S., "Passive Smoking Among Nonsmoking Women and the Relationship Between Indoor Air Pollution and Lung Cancer Incidence -- Results of a Multicenter

2023379894

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

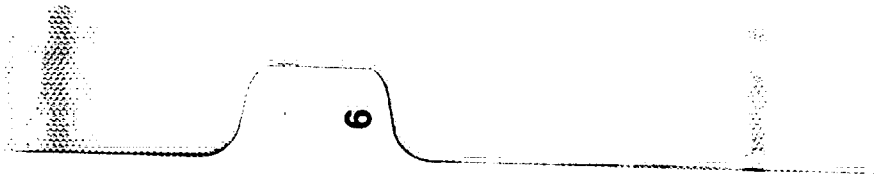
Case Controlled Study," Gan to Rinsho 36(3): 329-333, 1990 (translation).

28. Wu-Williams, A.H., Dai, X.D., Blot, W., Xu, Z.Y., Sun, X.W., Xiao, H.P., Stone, B.J., Yu, S.F., Feng, Y.P., Ershow, A.G., Sun, J., Fraumeni, J.F. and Henderson, B.E., "Lung Cancer Among Women in North-East China," British Journal of Cancer 62: 982-987, 1990.

29. Liu, Z., He, X. and Chapman, R.S., "Smoking and Other Risk Factors for Lung Cancer in Xuanwei, China," International Journal of Epidemiology 20(1): 26-31, 1991.

2023279895

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000



2023379896

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

OTHER STUDIES DISCUSSING LUNG CANCER

In addition to the primary lung cancer studies discussed in Section A of this notebook, there are several other studies which are sometimes mentioned in the context of epidemiologic studies on ETS and lung cancer. Because these studies are methodologically flawed or report incomplete data, they are of limited usefulness. For instance, the earlier studies (e.g., Knoth, et al., 1983; Miller, 1984; Sandler, et al., 1985) were excluded from the Letzel and Überla meta-analysis (1990), and even from the meta-analyses conducted by the National Academy of Sciences in 1986 and by the Environmental Protection Agency in 1990.

Following are brief summaries of each of these studies, focusing on their problems. Copies of these studies follow this introduction, arranged in chronological order and highlighted in yellow for useful information and in blue for adverse information.

Knoth, et al., 1983.

- This German study included a total of 792 lung cancer patients. There was no control population for comparison, and thus, the authors' conclusions are of limited value.[1]

- One reviewer commented that this report contained "only tentative conclusions based on poor data analyzed by

2023278897

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

unacceptable methods."[2]

Sandler, et al., 1985

- Although the papers published by Sandler, et al., in 1985 focused on overall mortality, some numbers of lung cancer deaths were presented.[3]

- The methodology and interpretation of these studies have been heavily criticized (e.g., one scientist described the studies as "heavily flawed").[4] The data presented are of limited value.

Dalager, et al., 1986.

- Data from three case-control studies conducted in the United States under the auspices of the National Cancer Institute were combined and analyzed in this study.[5] (Two of the studies, Correa, et al., and Buffler, et al., were discussed in Section A of this notebook.)

- Because the Dalager paper includes two primary studies on ETS and lung cancer, if it were included in considerations of the epidemiologic studies, it would result in some data being "counted" twice.

2023379898

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Lloyd, et al., 1986.

- In a study investigating the high rate of lung cancer in one town in Scotland, relatives of 42 cases who had died of lung cancer and of 42 matched controls who had died of other causes were interviewed.[6]

- Conclusions about ETS exposure were based on smokers and nonsmokers combined, thus precluding comparisons to the primary studies cited in Section A of this notebook. However, the authors reported no statistically significant differences between cases and controls for any questions relative to personal smoking or to ETS.

Katada, et al., 1988.

- This study, using hospitalized individuals in Nara, Japan, included only 25 female lung cancer cases (some of whom were smokers) and 50 female controls.[7]

- All of the cases reported present exposure to ETS, all but two reported past exposure, and all but four reported childhood exposure. Thus, the reference categories (i.e., non-exposed women) are too small to allow appropriate calculations of relative risk.

2023379899

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

- Nevertheless, none of the case-control comparisons was statistically significant at the 5% level. (Note: the paper also bases some of its conclusions on nonsmokers and smokers combined.)

Lam and Cheng, 1988

- This paper reviews four lung cancer studies previously conducted in Hong Kong, all of which are presented in the Primary Studies section of this notebook.[8]

- Using meta-analysis, Lam and Cheng calculate a statistically significant summary point estimate for the four studies.

Chen, et al., 1990

- In 1990, conclusions based on a study of 332 cases and 635 group-matched hospital controls in Taiwan were published.[9]

- For ETS exposure, point estimates achieving statistical significance were reported; however, it appears that these point estimates were calculated using both nonsmokers and active smokers, and are thus not comparable with other studies of nonsmokers only.

2023279900

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Miller, 1990.

- Miller used newspaper death notices to ascertain cancer deaths in women in northwestern Pennsylvania, and then interviewed surviving next-of-kin to obtain information on the deceased women. This approach could be expected to result in problems related to accurate recall by those interviewed.[10]

- In a 1984 paper, Miller examined "all cancer deaths" (See Other Cancers section in this notebook); in the 1990 paper, he provides numbers of cancer deaths by site.

2023379901

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Knoth, A., Bohn, H. and Schmidt, F., "Passive Smoking as a Causative Factor of Lung Cancer in Nonsmoking Women," Med Clin Prax 78(2): 56-59, 1983 (translation).

2. Heller, W., "Lung Cancer and Passive Smoking," Lancet II: 1309, 1983.

3. Sandler, D.P., Everson, R.B. and Wilcox, A.J., "Passive Smoking in Adulthood and Cancer Risk," American Journal of Epidemiology 121: 37-48, 1985.

   Sandler, D.P., Everson, R.B., Wilcox, A.J. and Browder, J.P., "Cancer Risk in Adulthood from Early Life Exposure to Parents' Smoking," American Journal of Public Health 75(5): 487-492, 1985.

   Sandler, D.P., Wilcox, A.J. and Everson, R.B., "Cumulative Effects of Lifetime Passive Smoking on Cancer Risk," Lancet II: 312-314, 1985.

4. Burch, P.R.J., "Lifetime Passive Smoking and Cancer Risk," Lancet II: 866, 1985.

   Higgins, I., "Lifetime Passive Smoking and Cancer Risk," Lancet II: 866-867, 1985.

   Lee, P.N., "Lifetime Passive Smoking and Cancer Risk," Lancet II: 1444, 1985.

   Burch, P.R.J., "Passive Smoking in Adulthood and Cancer Risk," American Journal of Epidemiology 123 (2): 368-369, 1986.

   Friedman, G., "Passive Smoking in Adulthood and Cancer Risk," American Journal of Epidemiology 123 (2): 367, 1986.

   Mantel, N., "Passive Smoking in Adulthood and Cancer Risk," American Journal of Epidemiology 123 (2): 367-368, 1986.

5. Dalager, N.A., Pickle, L.W., Mason, T.J., Correa, P., Fontham, E., Stemhagen, A., Buffler, P.A., Ziegler, R.G. and Fraumeni, J.F., "The Relation of Passive Smoking to Lung Cancer," Cancer Research 46: 4808-4811, 1986.

6. Lloyd, O.L., Ireland, E., Tyrrell, H. and Williams, F., "Respiratory Cancer in a Scottish Industrial Community: A Retrospective Case-Control Study," Journal of the Society for Occupational Medicine 36(1): 2-8, 1986.

2023379902

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

7. Katada, H., Mikami, R., Konishi, M., Koyama, Y. and Narita, N., "Effect of Passive Smoking in Lung Cancer Development in Women in the Nara Region," Gan No Rinsho 34(1): 21-27, 1988 (translation).

8. Lam, T.H. and Cheng, K.K., "Passive Smoking Is a Risk Factor for Lung Cancer in Never Smoking Women in Hong Kong," Smoking and Health 1987 eds. M. Aoki, S. Hisamichi and S. Tominaga (Amsterdam: Excerpta Medica, 1988): 279-281.

9. Chen, C.-J., Wu, H.-Y., Chuang, Y.-C., Chang, A.-S., Luh, K.-T., Chao, H.-H., Chen, K.-Y., Chen, S.-G., Lai, G.-M., Huang, H.-H. and Lee, H.-H., "Epidemiologic Characteristics and Multiple Risk Factors of Lung Cancer in Taiwan," Anticancer Research 10: 971-976, 1990.

10. Miller, G.H., "The Impact of Passive Smoking: Cancer Deaths Among Nonsmoking Women," Cancer Detection and Prevention 14(5): 497-503, 1990.

2023279903

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023379904

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

ETS AND
LUNG CANCER IN NONSMOKERS

VOLUME II

2023279905

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

CRITICISMS OF THE EPIDEMIOLOGIC STUDIES ON ETS AND LUNG CANCER

Some general criticisms are applicable to the majority of the epidemiologic studies on ETS and lung cancer.

Strength of the association

- Wynder and Kabat wrote in 1990:

> An association is generally considered weak if the odds ratio is under 3.0 and particularly when it is under 2.0, as is the case in the relationship of ETS and lung cancer.[1]

Such a weak association calls for special attention to possible sources of bias and confounding.

Exposure bias

- Spouses, next-of-kin or friends are sometimes asked to estimate the amount of ETS to which they think the subject was exposed. This may result in something called "exposure bias" or "exposure misclassification."[2]

- Exposure indices and risk estimates based on this type of information may be improper and incorrect.

- One example of this was reported in the Garfinkel, et al., study, published in 1985, which reported relative risks of 0.83 when the cases answered questions about ETS, 0.77 when

2023379906

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

the cases' husbands answered, and 3.57 when the cases' children answered (a copy of this study may be found in Section A of this notebook).

Reporting bias

- Another type of bias that may arise is "reporting bias," which may result if cases and controls respond differently to questions about personal smoking and ETS exposure.[2]

Publication bias

- "Publication bias" arises from the apparent failure by scientific journals to publish papers reporting negative or weakly positive results. If this occurs, the set of published investigations may not be truly representative of all the studies in the area.[3]

Confounding factors

- The studies did not always account for possible confounding factors. (This is addressed in more detail in the section in this notebook on confounders.)

2023379907

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Use of questionnaires

- All of the epidemiologic studies on the purported association between ETS exposure and disease in nonsmokers rely solely upon questionnaires about exposure, rather than upon actual exposure data.[4] Recent studies indicate that questionnaires are an unreliable and inaccurate measure of exposure.

- Questionnaire responses about exposure vary widely when compared with actual measurements of ETS constituents in the ambient air.[5]

Histology

- Lung cancer diagnoses were not always histologically or pathologically verified.[1]

- Also, the histological composition, i.e., the type of lung cancer, differed among studies (in some studies, all histological types were included; in others, some types were excluded).[1]

2023379908

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

"Data-dredging"

- Investigators often examine numerous subgroups of the study population, and may report only those conclusions which fit with their hypothesis.[1] (This is sometimes called "data-dredging.")

Misclassification

- If the personal smoking status of subjects is not accurately classified, it could result in "misclassification bias."

- One critic, Peter Lee, contends that the reported "risks" for nonsmokers are the result of bias caused by a small number of smokers who are reported in the studies as nonsmokers.[6]

Conclusion

German scientist Karl Überla discussed some criticisms of the ETS-lung cancer studies at a recent scientific symposium in Argentina:

> The majority of criteria for a causal connection are not fulfilled. There is no consistency, there is a weak association, there is no specificity, the dose-effect relation can be viewed controversially, bias and confounding are not adequately excluded, there is no intervention study, significance is only present under special conditions and the biological—

2023379909

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

plausibility can be judged controversially.[7]

The eminent statistician Nathan Mantel concluded the following:

> [I]t is unlikely that any epidemiological study has been, or can be, conducted which could permit establishing that the risk of lung cancer has been raised by passive smoking. Whether or not the risk is raised remains to be taken as a matter of faith.[3]

Copies of critical papers, highlighted in yellow for useful information and in blue for adverse statments, are found at Tabs 1-7.

2023379910

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

CRITICISMS OF THE HIRAYAMA STUDY

Numerous criticisms of the Hirayama study have been made.[8-21] They include:

- The age distribution of the sample is not representative of the total Japanese population, particularly for women over the age of 40.[8] When a statistical correction is made for this bias, the increased relative risk reported by Hirayama virtually disappears.

- The appropriateness of Hirayama's standardization of the data by husband's age, rather than by subject's, has been questioned.[9-12] When Kilpatrick re-analyzed the data adjusted by subject's age, the model used by Hirayama was shown to be inappropriate and the reported significantly elevated risk associated with husband's smoking was no longer apparent.

- The Hirayama study was not designed to investigate ETS exposure; it is inappropriate to use it to make conclusions about the hypothesis of an ETS-lung cancer relationship.[8]

- Errors and internal inconsistencies in the data and in risk ratios and confidence intervals have been noted and publicly acknowledged by Hirayama.[13-15]

2023279911

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

- The design of the study has been criticized, e.g., use of death certificates as evidence for lung cancer is unreliable[8]; autopsy or histology results were available for only 11.5% (23 of 200) of the cases[8,16]; use of the smoking status of the subject's husband as a surrogate measure for ETS exposure is not reliable[8,12]; many possible confounding factors were overlooked.[8,17]

It appears that Hirayama has never adequately addressed the criticisms; for instance, his 1990 monograph on the study persists in presenting the same data analyses that have been particularly criticized.[18] In addition, Hirayama has not made his original data available for review.[8,19,20]

A bibliography of the criticisms follows. Copies of selected papers are given at Tabs 8-20. They are highlighted in yellow for useful information and in blue for adverse statements.

2023379912

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

CRITICISMS OF THE TRICHOPOULOS STUDY

Regarding the Trichopoulos, et al., study, the following criticisms have been made:

- In 1990, Letzel and Überla evaluated the quality of ETS-lung cancer studies.[22] Based on possible sources of bias and other problems with study design, they concluded that the Trichopoulos, et al. study, in particular, is "methodologically unacceptable" and is "a textbook example of how a case-control study should not be performed." Furthermore, they reported that this study may strongly influence the outcomes of meta-analyses of the ETS-lung cancer epidemiological studies (e.g., when the Trichopoulos study was included in meta-analyses of all possible case-control study combinations, it appeared in 330 of the 353 significant study combinations).

- Methodologically, the study has been criticized for selecting cases and controls from different hospitals; for excluding patients with adenocarcinoma and with alveolar carcinoma; for the lack of histological or cytological confirmation in 35% of the cases; and for its small sample size.[8,24] According to Überla, the small sample size means that "the statistically 'significant' results of this study may well be artefacts from chance, bias or confounding."[23]

2023379913

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Copies of the articles referenced above, highlighted in yellow for useful information and in blue for adverse statements are found at Tabs 21-23.

2023279914

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES
General Criticisms

1. Wynder, E.L. and Kabat, G.C., "Environmental Tobacco Smoke and Lung Cancer: A Critical Assessment," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 5-15.

2. Kilpatrick, S.J., "Misclassification of Environmental Tobacco Smoke Exposure: Its Potential Influence of Studies of Environmental Tobacco Smoke and Lung Cancer," Toxicology Letters 35: 163-168, 1987.

3. Mantel, N., "Lung Cancer and Passive Smoking," British Medical Journal 294: 440, 1987.

   Newcombe, R., "Towards a Reduction in Publication Bias," British Medical Journal 295: 656-659, 1987.

4. Coultas, D.B., Peake, G.T. and Samet, J.M., "Questionnaire Assessment of Lifetime and Recent Exposure to Environmental Tobacco Smoke," American Journal of Epidemiology 130(2): 338-347, 1989.

   Coultas, D.B., Samet, J.M., McCarthy, J.F. and Spengler, J.D., "A Personal Monitoring Study to Assess Workplace Exposure to Environmental Tobacco Smoke," American Journal of Public Health 80(8): 988-990, 1990.

5. Coultas, D.B., Samet, J.M., McCarthy, J.F. and Spengler, J.D., "Variability of Measures of Exposure to Environmental Tobacco Smoke in the Home," American Review of Respiratory Disease 142: 602-606, 1990.

6. Lee, P.N., "Increased Risk of Lung Cancer in Non-smokers Married to Smokers: A Result of ETS Exposure or of Bias?" Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 25-36.

7. Überla, K., "Epidemiology: Its Scope and Limitations for Indoor Air Quality," Indoor Air Quality (Buenos Aires: National Academy of Sciences of Buenos Aires, Argentina, 1988): 45-60.

2023379915

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES
Criticisms of Hirayama, 1981

8. Überla, K. and Ahlborn, W., "Passive Smoking and Lung Cancer: A Reanalysis of Hirayama's Data," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 333-340.

9. MacDonald, E., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 915-916, 1981.

   MacDonald, E., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 1465, 1981.

10. Lee, P., "Passive Smoking," Food Chemistry and Toxicology 20: 223-229, 1982.

11. Kilpatrick, S. and Viren, J., "Age as a Modifying Factor in the Association Between Lung Cancer in Non-Smoking Women and Their Husbands' Smoking Status," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk (London: Selper, Ltd., 1988): 195-202.

12. Kilpatrick, S., "An Example of Extra-Poisson Variation Suggesting an Under-Specified Model," Present and Future of Indoor Air Quality, eds. C. Bieva, Y. Courtois and M. Govaerts (Amsterdam: Excerpta Medica, 1989): 83-90.

    Kilpatrick, S., "Model Specification Effects in ETS/Nutrition Research," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 257-271.

13. Lee, P., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 1465-1466, 1981.

14. Hirayama, T., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 1466, 1981.

15. Layard, M. and Viren, J., "Assessing the Validity of a Japanese Cohort Study," Present and Future of Indoor Air Quality, eds. C. Bieva, Y. Courtois and M. Govaerts (Amsterdam: Excerpta Medica, 1989): 177-180.

16. Grundmann, E., Miller, K.-M. and Winter, K.D., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal I, 282: 1156, 1981.

2023379916

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

17. Sterling, T., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal I, 282: 1156, 1981.

18. Hirayama, T., Life-Style and Mortality: A Large-Scale Census-Based Cohort Study in Japan, (Basel: Karger, 1990).

19. Adlkofer, F., "Probleme mit dem Passivrauchen (The Problems of Passive Smoking)," Der Kassenarzt 27(51/52): 29-39, 1987. Translation.

20. Ahlborn, W. and Überla, K., "Passive Smoking and Lung Cancer: Reanalyses of Hirayama's Data," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk (London: Selper, Ltd., 1988): 169-178.

21. Aviado, D., "Toxicological Basis for Regulation of Indoor Air Quality," Journal of Applied Toxicology 8(3): 155-157, 1988.

Diamond, G. and Forrester, J., "Clinical Trials and Statistical Verdicts: Probable Grounds for Appeal," Annals of Internal Medicine 98(3): 385-394, 1983.

Gostomzyk, G., "Krank durch Passivrauchen (Disease Due to Passive Smoking?)," Munch med Wschr 124(4):16, 1982. Translation.

Kornegay, H. and Kastenbaum, M., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 914, 1981.

Mantel, N., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 914-915, 1981.

Mantel, N., "Epidemiologic Investigations: Care in Conduct, Care in Analysis, and Care in Reporting," Journal of Cancer Research and Clinical Oncology 105: 113-116, 1983.

Rutsch, M., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal I, 282: 985, 1981.

2023279917

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES
Criticisms of Trichopoulos, et al., 1981

22. Letzel, H. and K. Überla, "Meta-Analyses on Passive Smoking and Lung Cancer," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 316-322.

23. Überla, K., "Lung Cancer from Passive Smoking: Hypothesis or Convincing Evidence?," International Archives of Occupational and Environmental Health 59: 421-437, 1987.

24. Heller, W.-D., "Lung Cancer and Passive Smoking," The Lancet II: 1309, 1983.

2023379918

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023379919

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

CONFOUNDING FACTORS

Introduction

According to a 1990 publication by a Swedish scientist, Dr. Ragnar Rylander:

> Studies evaluating the hypothesis of a relationship between exposure to environmental tobacco smoke and lung cancer must take into account other environmental risk or protection factors and the possibility that exposure to environmental tobacco smoke may be confounded. This has not been done in the majority of such studies. Until this has been done, the claim of causality between environmental tobacco smoke and lung cancer remains uncertain. [Emphasis added.][1]

In epidemiologic studies, confounders are variables which can affect the outcome of interest, independently of the factor under investigation. Potential confounding factors in studies of ETS and lung cancer are numerous and varied.[2] It is difficult to control for all of them in the design of an epidemiologic study. Following are lists of some of the possible confounders encountered in epidemiologic studies of lung cancer incidence in nonsmokers, both those specifically considering ETS and those dealing with other factors.

2023379920

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Heating and Cooking Fuels

- In developing countries, the use of certain fuels (kerosene, gas, coal, liquefied petroleum gas, straw, or wood) for heating and cooking contributes to elevated levels of indoor air pollution, which may contribute to disease incidence.[3]

- Following earlier, limited reports[4] on exposures to fumes from the use of various fuels, eight studies examining coal use in stoves and other indigenous heating devices in China have recently been published.[5-12] RRs as high as 14 have been reported,[8] although most RRs are in the 1.0 to 2.0 range.[11,12]

- Some fuels, namely, kerosene or coal and wood or straw, have been associated with a increased risk of lung cancer in Japanese women as well.[13,14]

Cooking Techniques

- The use of certain cooking oils and some cooking techniques (i.e, stir-frying and deep frying) which produce oil vapors have been associated with increased lung cancer risks in Chinese women.[11,15]

2023379921

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Air Pollution

- In addition to indoor air pollution from heating and cooking fuels, as described above, outdoor air pollution has been associated with increased lung cancer incidence in at least one epidemiologic study in northeast China.[12]

Dietary Factors

- Increased lung cancer risk has been associated with the consumption of smoked, salted, cured, pickled, processed, or spicy foods among Oriental women.[18] Additionally, research suggests that wives whose husbands smoke may consume more processed and spicy foods and eat fewer fresh fruits and vegetables than do those whose husbands do not smoke.

- One study reported an elevated lung cancer risk among Oriental women associated with the consumption of green or black tea.[17]

- It has also been reported that nonsmokers married to smokers have lower intakes of dietary carotene, a substance associated with decreased cancer risks when consumed in sufficient amounts.[18] Recently, an abstract reported an correlation between serum carotene levels and socioeconomic status; this

2023279922

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

could be important if smoking and SES are also correlated, as has been suggested.

Occupation

- Some of the studies considering lung cancer in nonsmokers have also reported elevated relative risks associated with employment in certain fields or with occupational exposures to certain substances.[5,11-13]

Medical and Lifestyle Factors

- Personal health factors such as menstrual cycle length and previous history of respiratory disease (including tuberculosis, pneumonia or emphysema) have been associated with increased risk for lung cancer.[5,9,11,15]

- Family history of lung cancer has also been associated with increased lung cancer risk.[9,11]

- An association between husband's smoking status and family lifestyle has been reported.[16] Wives with husbands who were nonsmokers had better SES, were more conscientious housewives, ate better diets, had higher indices of family cohesiveness,

2023379923

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

and had better indices of overall health than did women married to smokers.

- At least one hobby, keeping pet birds, has been associated with increased lung cancer risk.[19]

Conclusion

While of general importance, the question of confounders appears to be particularly relevant in studies of Asian women. Certain cultural variables (e.g., use of smoky fuels, certain cooking methods, diet) differ greatly between Asian and Western populations. The potential effects of such factors must be considered when evaluating the results of epidemiologic studies on lung cancer incidence, particularly those considering ETS exposure. Table 1 presents a comparison and summary of Asian studies to date, revealing the increasing attention paid to confounders in these studies.

Dr. Linda Koo, in her 1988 paper on lifestyle correlates, summed up the importance of confounders as follows:

> [C]aution should be exercised when interpreting data on ETS. It may not be the hazards of tobacco smoke that are being evaluated, but a whole range of behaviors that result from having a smoking husband, which may in turn increase the risk for certain diseases among their wives and children.[16]

2023379924

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Table 1a. Asian Studies Included in EPA Draft Risk Assessment: Epidemiologic Studies of Lung Cancer in Nonsmoking Women, with Spousal Smoking Included

Study [site]	Sample Size	Spousal Smoking*	Factors Considered: Heating Methods/ Fuel Use	Cooking Tech-Niques	Diet	Other
Hirayama, 1981, 1984 [Japan]	91,540	(+)	--	--	--	--
Chan and Fung, 1982 [Hong Kong]	223	(-)	--	Yes	--	--
Lam, 1985 [Hong Kong]	248	(-)	--	Yes	--	Home incense burning
Akiba, et al., 1986 [Japan]	1,385	(+)	--	--	--	Radiation exposure
Gao, et al., 1987 [Shanghai]	1,407	(-)	--	Yes	Yes	Medical history; hormonal factors
Koo, et al., 1987 [Hong Kong]	225	(-)	--	--	--	--
Lam, et al., 1987 [Hong Kong]	890	(+)	--	--	--	--
Geng, et al., 1988 [Tianjin, China]	314	(+)	Yes	--	--	Medical history; occupation
Inoue and Hirayama, 1988 [Japan]	83	(+)	--	--	--	--

2023379925

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Study [site]	Sample Size	Spousal Smoking*	Factors Considered: Heating Methods/ Fuel Use	Cooking Tech= Niques	Diet	Other
Shimizu, et al., 1988 [Japan]	180	(-)	Yes	--	Yes	Occupation

* (+) indicates a statistically significant relative risk was reported; (-) indicates the reported relative risk was not statistically significant.

2023379926

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Table 1b. Asian Studies Published After EPA Draft Risk Assessment: Epidemiologic Studies of Lung Cancer in Nonsmoking Women, with Spousal Smoking Included

Study [site]	Sample Size	Spousal Smoking*	Factors Considered: Heating Methods/ Fuel Use	Cooking Tech-Niques	Diet	Other
He, et al., 1990 [China]	536+	(-)	Yes	Yes	--	Medical history
Sobue, et al., 1990 [Japan]	639	(-)	Yes	--	--	--
Wang, et al., 1990 [NE China]	110	(-)	Yes	--	--	Indoor and outdoor air pollution
Wu-Williams, et al., 1990 [NE China]	1,924	(+)**	Yes	Yes	Yes	Medical history; occupation
Liu, et al., 1991*** [China]	221	(-)	Yes	Yes	--	Medical history

* (+) indicates a statistically significant relative risk was reported; (-) indicates the reported risk was not statistically significant.
\+ Males and females combined.
** The reported relative risk was statistically significantly negative.
***Full report on population discussed in He, et al., abstract.

2023379927

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Table 1c. Ancillary Asian Studies, Not Considered in EPA Draft Risk Assessment

Study [site]	Sample Size	Factors Considered: Spousal Smoking	Heating Methods/ Fuel Use	Cooking Tech-Niques	Diet	Other
Koo, et al., 1984 [Hong Kong]	400	No**	--	--	--	--
Mumford, et al., 1987 [China]	--	No	Yes	--	--	--
Chapman, et al., 1988 [China]	144+	No	Yes	--	--	--
Koo, et al., 1988 [Hong Kong]	136	No	--	--	Yes	Lifestyle variables
Du and Ou, 1990 [China]	1,324	No	Yes	--	--	--
Xu, et al., 1990 [NE China]	1,077	No	Yes	Yes	Yes	Indoor and outdoor air pollution; occupation

2023799928

** Other questions were asked regarding ETS.
+ Males and females combined.

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

A selection of the relevant literature follows. Useful information is highlighted in yellow; problematic statements are highlighted in blue.

2023279929

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Rylander, R., "Environmental Tobacco Smoke and Lung Cancer," The New England Journal of Medicine 323(12): 834, 1990.

2. Katzenstein, A.W., "An Estimate of Adult Mortality in the United States from Passive Smoking: A Response," Environment International 16: 175-193, 1990.

3. Chen, B.H., Hong, C.J., Pandey, M.R. and Smith, K.R., "Indoor Air Pollution in Developing Countries," World Health Statistics Quarterly 43: 127-138, 1990.

4. Anonymous, "Lung Cancer in South China," Oncology Times 7(6): 33, 1986.

   deSerres, F.J. and Matsushima, T., "Meeting Report: Mutagenesis and Carcinogenesis by Nitropyrenes and Cancer Chemotherapeutics," Mutation Research 164: 3-8, 1986.

5. Geng, G.-Y., Liang, T.H., Zhang, A.Y. and Wu, G.L., "On the Relationship Between Smoking and Female Lung Cancer," Smoking and Health 1987, eds. M. Aoki, S. Hisamichi and S. Tominaga (Amsterdam: Excerpta Medica, 1988): 283-285.

6. Mumford, J.L., He, X.Z., Chapman, R.S., Cao, S.R., Harris, D.B., Li, X.M., Xian, Y.L., Jiang, W.Z., Xu, C.W., Chuang, J.C., Wilson, W.E. and Cooke, M., "Lung Cancer and Indoor Air Pollution in Xuan Wei, China," Science 235: 217-220, 1987.

7. Chapman, R.S., Mumford, J.L., Harris, D.B., He, X., Jiang, W. and Yang, R., "The Epidemiology of Lung Cancer in Xuan Wei, China: Current Progress, Issues and Research Strategies," Archives of Environmental Health 43(2): 180-185, 1988.

8. Du, Y.-X. and Ou, X.-L., "Indoor Air Pollution and Woman Lung Cancer," Indoor Air '90: Proceedings of the 5th International Conference on Indoor Air Quality and Climate, Toronto, Canada, July 29-August 3, 1990.

9. Liu, Z., He, X., and Chapman, R.S., "Smoking and Other Risk Factors for Lung Cancer in Xuanwei, China," International Journal of Epidemiology 20(1): 26-31, 1991.

   He, X., Chen, W., Liu, Z. and Chapman, R.S., "An Epidemiological Study of Lung Cancer in Xuan Wei County, China: Current Progress," (abstract), presented at the Second Annual Meeting of the International Society for Environmental Epidemiology, Berkeley, California, August 13-15, 1990.

2023239930

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

10. Wang, F.-L., et al., "Analysis of Risk Factors for Female Lung Adenocarcinoma in Haerbin: Indoor Air Pollution," Chinese Journal of Preventive Medicine 23(5): 270-273, 1989 (translation).

11. Wu-Williams, A.H., Dai, X.D., Blot, W., Xu, Z.Y., Sun, X.W., Xiao, H.P., Stone, B.J., Yu, S.F., Feng, Y.P., Ershow, A.G., Sun, J., Fraumeni, J.F. and Henderson, B.E., "Lung Cancer Among Women in North-East China," British Journal of Cancer 62: 982-987, 1990.

12. Xu, Z.-Y., Blot, W.J., Xiao, H.-P., Wu, A., Feng, Y.-P., Stone, B.J., Sun, J., Ershow, A.G., Henderson, B.E. and Fraumeni, J.F., "Smoking, Air Pollution, and the High Rates of Lung Cancer in Shenyang, China," Journal of the National Cancer Institute 81: 1800-1806, 1989.

13. Shimizu, H., Morishita, M., Mizuno, K., Masuda, T., Ogura, Y., Santo, M., Nishimura, M., Kunishima, K., Karasawa, K., Nishiwaki, K., Yamamoto, M., Hisamichi, S. and Tominaga, S., "A Case-Control Study of Lung Cancer in Nonsmoking Women," Tohoku Journal of Experimental Medicine 154: 389-397, 1988.

14. Sobue, T., Suzuki, R., Nakayama, N., Inubuse, C., Matsuda, M., Doi, O., Mori, T., Furuse, K., Fukuoka, M., Yasumitsu, T., Kuwabara, O., Ichigaya, M., Kurata, M., Kuwabara, M., Nakahara, K., Endo, S. and Hattori, S., "Passive Smoking Among Nonsmoking Women and the Relationship Between Indoor Air Pollution and Lung Cancer Incidence -- Results of a Multicenter Case Controlled Study," Gan to Rinsho 36(3): 329-333, 1990 (translation).

15. Gao, Y.-T., Blot, W.J., Zheng, W., Ershow, A.G., Hsu, C.W., Levin, L.I., Zhang, R. and Fraumeni, J.F., "Lung Cancer Among Chinese Women," International Journal of Cancer 40: 604-609, 1987.

16. Koo, L.C., "Dietary Habits and Lung Cancer Risk Among Chinese Females in Hong Kong Who Never Smoked," Nutrition and Cancer 11: 155-172, 1988.

Koo, L.C., Ho, J.H.-C. and Rylander, R., "Life-History Correlates of Environmental Tobacco Smoke: A Study on Nonsmoking Hong Kong Chinese Wives with Smoking Versus Nonsmoking Husbands," Soc Sci Med 26(7): 751-760, 1988.

Koo, L.C., "Environmental Tobacco Smoke and Lung Cancer: Is It the Smoke or the Diet?" Present and Future of Indoor Air

2023279931

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Quality, C.J. Bieva, et al., (eds.), (Amsterdam: Excerpta Medica, 1989): 65-75.

17. Tewes, F.J., Koo, L.C., Meisgen, T.J. and Rylander, R., "Lung Cancer Risk and Mutagenicity of Tea," Environmental Research 52: 23-33, 1990.

18. Sidney, S., Caan, B.J. and Friedman, G.D., "Dietary Intake of Carotene in Nonsmokers with and Without Passive Smoking at Home," American Journal of Epidemiology 129(6): 1305-1309, 1989.

Waller, K.D. and Smith, A.H., "Effects of Socioeconomic Status and Smoking on Serum Beta-Carotene," Archives of Environmental Health 46(2): 120, 1991.

19. Holst, P.A., et al., "For Debate: Pet Birds as an Independent Risk Factor for Lung Cancer," British Medical Journal 297: 1319-1321, 1988.

2023279932

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023379933

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

USE OF META-ANALYSIS: EPIDEMIOLOGIC STUDIES ON ETS AND LUNG CANCER

Introduction

The statistical procedure of meta-analysis treats the results of individual studies as individual data points in an overall analysis. It has been used effectively in combining the results of randomized, controlled clinical trials of pharmaceuticals. Such studies are eminently comparable because their methodologies and study populations are very similar.

More recently, meta-analysis has been used to analyze the results of epidemiologic studies, that is, to calculate an overall relative risk as a weighted average of the relative risks of many studies. Because of the inherent differences in study design, methodology, and sample population, especially in the case of epidemiologic studies on ETS and lung cancer, questions have been raised regarding the appropriateness of using this procedure to analyze epidemiologic data. However, meta-analysis is still being used; most recently, the U.S. Environmental Protection Agency (EPA) used a meta-analysis to calculate an estimated overall relative risk for lung cancer related to exposure to environmental tobacco smoke (ETS).[1]

The EPA meta-analysis is not the first in this area. The risk estimates calculated by several other meta-analyses are given in Table 1 for comparison.[2-8]

2023279934

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

In addition to its meta-analysis on United States ETS-lung cancer studies, the recent paper by Fleiss and Gross (1991) presents a detailed criticism of the meta-analytical method, particularly as applied to the ETS literature.[8] This is a thorough review paper and a useful reference. Some relevant quotations follow:

> [T]he authors of the NRC report appear not to have followed the major guidelines proposed by Sacks, et al. For example, they did not provide a formal protocol for the meta-analysis, nor, apparently, did they give any consideration to the possibility of heterogeneous ORs across the several studies. (p. 134)
>
> Furthermore, the question comes to mind whether the existing epidemiological studies of a possible association between exposure to ETS and the incidence of lung cancer in non-smokers are of adequate quality. Indeed, there is the question whether any of these studies meets even minimal standards of quality. (pp. 134-135)
>
> There are many reasons for restricting attention to American studies of whether there is an elevated risk of lung cancer to non-smokers exposed to ETS relative to non-smokers not so exposed. One is that this is the population to whom policy decisions will apply and on whom those decisions should be based. (p. 135)
>
> Odds ratios from studies in other countries, on the other hand, are derived from distributions that may differ markedly from those in the U.S., and thus the ORs themselves may not be relevant to the American experience. Genetic and lifestyle differences between the U.S. population and the populations studied elsewhere (mainly in east Asia) also argue for a meta-analysis only of U.S. studies. (p. 135)

2023379935

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

> [U]ncritical use of meta-analysis can and does lead to unsubstantiated conclusions. Only when all the issues that we have discussed are considered and possibly accounted for is it possible to apply meta-analysis so that the overall result is scientifically valid. (p. 137)
>
> It is very unlikely that the biases present in the epidemiological studies of the possible association between exposure to ETS and the risk of lung cancer can ever be removed. The meta-analysis performed by the NRC must either be completely discounted or, as Stein concluded so succinctly in another context, considered a mere 'computational exercise.' (p. 137)

(An editorial comment on this paper by Spitzer is also included.[9])

Copies of some of the referenced articles are included at Tabs 1-4. They are highlighted in yellow for useful information, and in blue for adverse information.

2023279936

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Table 1. Results of Meta-Analyses of Epidemiologic Studies of Spousal Smoking and Female Lung Cancer

Meta-Analysis	Summary Risk Estimate	Studies Included
Wald, et al., 1986	1.35 (95% CI 1.19-1.54)	13; 10 case-control, 3 cohort
NRC, 1986	1.32 (95% CI 1.16-1.51)	13; 10 case-control, 3 cohort
Blot and Fraumeni, 1986	1.3 (95% CI 1.1-1.5)	12; 10 case-control, 2 cohort
Wells, 1988	1.44 (95% CI 1.26-1.66)	17; 14 case-control, 3 cohort
EPA, 1990	1.41 (95% CI 1.26-1.57)	22; 19 case-control, 3 cohort
	1.25 (95% CI 1.03-1.52)	8 U.S. studies; 7 case-control, 1 cohort
Letzel and Überla, 1990	1.118 1.076	12; 10 case-control, 2 cohort 11; 9 case-control (Trichopoulos excluded), 2 cohort
Fleiss and Gross, 1991	1.12 (95% CI 0.95-1.30)	9 U.S. studies; 8 case-control, 1 cohort
Layard and LeVois, 1991 (unpublished)	1.08 (95% CI 0.96-1.22)	26; 23 case-control, 3 cohort

2023799337

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. United States Environmental Protection Agency, "Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children," (Review Draft) EPA/600/6-90/006A, May, 1990.

2. Wald, N.J., Nanchahal, K., Thompson, S.G. and Cuckle, H.S., "Does Breathing Other People's Tobacco Smoke Cause Lung Cancer?," British Medical Journal 293: 1217-1222, 1986.

3. National Research Council, Environmental Tobacco Smoke: Measuring Exposure and Assessing Health Effects (Washington: National Academy Press, 1986).

4. Blot, W.J. and Fraumeni, J.F., "Passive Smoking and Lung Cancer," Journal of the National Cancer Institute 77(5): 993-1000, 1986.

5. Wells, A.J., "An Estimate of Adult Mortality in the United States from Passive Smoking," Environment International 14: 249-265, 1988.

6. Letzel, H. and Überla, K., "Meta-Analyses on Passive Smoking and Lung Cancer," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 316-322.

7. Layard, M.W. and LeVois, M.E., Letter to Dr. Donald G. Barnes, Director of the Science Advisory Board, United States Environmental Protection Agency, April 9, 1991.

8. Fleiss, J.L. and Gross, A.J., "Meta-Analysis in Epidemiology, with Special Reference to Studies of the Association Between Exposure to Environmental Tobacco Smoke and Lung Cancer: A Critique," Journal of Clinical Epidemiology 44(2): 127-139, 1991.

9. Spitzer, W.O., "Meta-Meta-Analysis: Unanswered Questions About Aggregating Data," Journal of Clinical Epidemiology 44(2): 103-107, 1991.

2023279938

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023379939

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

RISK ESTIMATES FOR NONSMOKER LUNG CANCER BASED UPON MODELING PROCEDURES

- In 1985, Repace and Lowrey published an article claiming that exposure to ETS is responsible for 500 to 5,000 lung cancer deaths per year in the United States.[1] This report received extensive press coverage upon its release.

- The report contains two highly theoretical models for estimating risks of lung cancer from ETS exposure. One model relies upon a "reinterpretation" of the epidemiologic studies of lung cancer in nonsmokers; the second model estimates lung cancer mortality among nonsmokers based on a single study dealing with the Seventh Day Adventists, a religious group known for its vigorous opposition to smoking.

- Critics of the Repace and Lowrey approach have pointed out that the estimates are based on errors and "unrealistic assumptions" which result in overestimations of exposure.[2] One analysis of the model showed that, depending on the assumptions and input data used, the estimates are inherently inaccurate and may vary by as much as 300-fold.[3] Another scientist noted that the exposure and dose levels used in the modeling exercise were not based on actual measurements; such measurements reported elsewhere range from "ten- to one-hundred-fold less than that in the Repace and Lowrey model."[4]

2023379940

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

- Other criticisms have focused on the report's methods of analysis,[5-7] and suggest that Repace and Lowrey failed to control for other confounding factors, and that their model did not provide "the very statistical bases of estimation procedures."[4]

- Repace and Lowrey's estimate of nonsmoker lung cancer risks in the workplace was also criticized by scientists who noted that none of the epidemiologic studies of ETS exposure and disease in nonsmoking working women report a statistically significant increase in risk.[2]

- Two British researchers, Darby and Pike, published a paper in 1988 describing another type of mathematical model which predicted potential effects from ETS exposure based on data from a study on active smoking.[8] Even when adjustments were made for childhood exposure to ETS, the authors reported that the model predicted a risk for nonsmokers that was smaller than "the underlying background risk for lung cancer." They concluded that their model could not explain the difference between risks reported for nonsmokers in epidemiologic studies and the low levels of ETS exposure reported in other studies.

2023279941

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

The Darby and Pike model was criticized in 1990 by Wald, et al., authors of one of the earlier meta-analyses on the epidemiologic studies of ETS exposure and lung cancer incidence.[9] Wald's group questioned Darby and Pike's conclusion that there was a discrepancy between risks estimated by epidemiologic studies and by exposure data. Darby and Pike replied that the existing cotinine data employed by Wald, et al., were possibly both insufficient and inappropriate to allow an adequate comparison to be made with the epidemiologic data.[10]

2023279942

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Repace, J.L. and Lowrey, A.H., "A Quantitative Estimate of Nonsmokers' Lung Cancer Risk from Passive Smoking," Environment International 11(1): 3-22, 1985.

2. Arundel, A., Irwin, T. and Sterling, T., "Nonsmoker Lung Cancer Risks from Tobacco Smoke Exposure: An Evaluation of Repace and Lowrey's Phenomenological Model," Journal of Environmental Science and Health C4(1): 93-118, 1986.

3. Arundel, A., Sterling, T. and Weinkam, J., "Never Smoker Lung Cancer Risks from Exposure to Particulate Tobacco Smoke," Environment International 13: 409-426, 1987.

4. Lebowitz, M.D., "The Potential Association of Lung Cancer with Passive Smoking," Environment International 12: 3-9, 1986.

5. Johnson, C. and Letzel, H., "Letter to the Editors," Environment International 12: 21-22, 1986.

6. Burch, P.R.J., "Health Risks of Passive Smoking: Problems of Interpretation," Environment International 12: 23-28, 1986.

7. Kilpatrick, S.J., "Letter to the Editors," Environment International 12: 29-31, 1986.

8. Darby, S.C. and Pike, M.C., "Lung Cancer and Passive Smoking: Predicted Effects from a Mathematical Model for Cigarette Smoking and Lung Cancer," British Journal of Cancer 58: 825-831, 1988.

9. Wald, N., Nanchahal, K., Cuckle, H. and Thompson, S., "Letter to the Editor: Lung Cancer and Passive Smoking," British Journal of Cancer 61: 337, 1990.

10. Darby, S.C. and Pike, M.C., "Response to the Letter from Dr. Wald," British Journal of Cancer 61: 337-338, 1990.

2023379943

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023379944

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

ETS AND CANCER OF SITES OTHER THAN THE LUNG

Introduction

A presenter at the recent McGill Symposium in Montreal, Canada, described the then-available epidemiologic studies on ETS and cancer other than the lung as follows:

> These nine studies provide insufficient data to evaluate the effect of ETS on cancer other than of the lung. The reported associations are weak and inconsistent, and are subject to the potential effects of biases and uncontrolled confounding factors . . .[1]

These studies concern a variety of cancer sites; the publications on each are briefly summarized below. Highlighted copies of the papers on cancer at other sites are found at Tabs 1-11.

All Cancers Combined

- Several studies have presented risk estimates for overall cancer incidence, regardless of site, among individuals reporting ETS exposure. This procedure disregards differences in etiology, mechanism and confounding factors among the various types of cancer; nevertheless, some authors have presented data in this fashion.

Hirayama (1984) reported a significant elevation in risk for "cancer of all sites," in nonsmoking women whose husbands

2023279945

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

smoked; he attributed the elevation to increased risks for lung, nasal sinus, and brain cancers.[2]

Miller (1984) reports on a "case-control" study conducted in Pennsylvania by interviewing the surviving relatives of women whose death notices were published in a local newspaper.[3] Miller reported an overall odds ratio of 1.40 for "death due to cancer" among women whose husbands smoked. Questions can be asked about the accuracy of the amount of recall required of the relatives in this study.

In an abstract, Reynolds, et al., (1987) reported that a record-linkage study in Alameda County, CA concluded that nonsmoking women married to smokers had a 70% higher risk of cancer incidence at all sites, and that they had an approximate relative risk of 7.0 for "smoking-related cancers."[4] The abstract provides insufficient information to judge the quality of the study; the reported risk estimates should be viewed with caution.

Sandler, et al., (1989) reported statistically nonsignificant point estimates of 1.01 (males) and 1.00 (females) for all cancers in persons reporting ETS exposure.[5] The authors' subdivision of the category into "smoking-related" and "other" cancers yielded no statistically significant risk estimates. This study was criticized by Holcomb (1989) as being "poor science" and

2023279946

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

"inadequately designed."[6]

Brain and Nasal Sinus Cancers

- A single report claims to show an increased risk for brain and nasal sinus cancers associated with marriage to a smoker. No other researchers have been able to replicate these findings and they must be considered isolated.

Only Hirayama (1984), reporting further on his study of Japanese women, has reported statistically significant associations in women between brain and nasal sinus cancers and spousal smoking.[2]

Breast Cancer

- Some claims have been made for a relationship between husband's smoking and breast cancer in nonsmoking women.

Sandler, et al., (1985) reported a statistically non-significant increased risk for breast cancer in non-smoking women and statistically significant elevated risks for cancers of the endocrine system associated with early life (i.e., childhood) exposure to parental smoking.[7]

2023379947

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Hirayama (1984), in his discussion of his claim that his data support an elevated risk for all cancers in nonsmoking women whose husbands smoke, suggested that part of the reported increase might be due to breast cancer.[2] In a 1991 article, Wells reports a statistically nonsignificant increased risk of breast cancer using additional data supplied by Hirayama.[8]

Bladder Cancer

- Two case-control studies have specifically examined bladder cancer incidence; neither reported an association between bladder cancer and exposure to ETS at home or at work.

The 1986 Kabat, et al., paper reported that cases and controls in this study did not differ significantly in reporting "sidestream smoke exposure" at home, at work or in transportation.[9] Neither did they differ significantly in whether or not their spouse smoked. The authors concluded that "exposure to sidestream smoke" is not an important factor in bladder cancer in nonsmokers.

The second study to report on bladder cancer is by Burch et al. (1989).[10] It was conducted in Alberta and Ontario, Canada. None of the reported relative risks was statistically significant. The authors concluded that there was no evidence for an effect of

2023279948

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

"passive smoking" on bladder cancer incidence in smokers or nonsmokers.

Cervical Cancer

- Two studies have reported on ETS exposure and the incidence of cervical cancer. Both fail to account sufficiently for confounding factors.

Statistically significant elevated risks for cervical cancer were reported in a 1985 study by Sandler, et al., of patients in North Carolina.[11] This study has been criticized because it did not control for known risk factors such as sexual activity, which is strongly correlated with incidence of cervical cancer.

Slattery, et al., (1989), in a study of women in Utah, reported a statistically significant increased risk of cervical cancer in non-smokers who reported three or more hours of ETS exposure per day (risk estimate of 3.43, 95% CI 1.23-9.54).[12] Although the researchers adjusted for age, church attendance, education and number of sexual partners, these variables do not account for all factors that may contribute to disease.

2023279949

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Zang, Wynder and Harris authored a letter in response to the Slattery, et al., study.[13] They wrote:

> [T]here clearly is undermatching of control patients with regard to important risk factors including sexual activity, religious background, and education. . . . Since the previously mentioned risk factors are correlated highly with one another as well as with active and passive smoking, the risk estimates relating smoking and cervical cancer may be subject to substantial bias and confounding. . . . In fact, the adjusted odds ratios are probably no more than the leftover effect of variables controlled imperfectly by logistic regression.

In a response, Slattery acknowledged that her group's conclusions "should be verified in other studies."[14]

Childhood Cancers

- Two papers have claimed that their data show that childhood exposure to ETS is related to increased incidence of certain childhood cancers.

Grufferman, et al., (1982) reported a statistically significant relative risk of 3.9 (95% CI 1.5-9.6) for father's cigarette smoking for childhood rhabdomyosarcoma in a case-control study in North Carolina.[15] Only 33 cases were included in the study; only 23 cases were included in the analysis of father's smoking. Conversely, for the 8 cases with maternal smoking, the reported relative risk was 0.8 (95% CI 0.3-2.0). An extremely

2023379950

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

large number of analyses was conducted in this study, suggesting the possibility of data-dredging.

A recent study (John, et al., 1991) reported associations for father's smoking during pregnancy (i.e., a surrogate for ETS exposure of the pregnant woman) in the absence of maternal smoking, with several indices of childhood cancer: all cancers combined (OR = 1.2, 95% CI 0.8-2.1), acute lymphocytic leukemia (OR = 1.4, 95% CI 0.6-3.1), lymphomas (OR = 1.6, 95% CI 0.5-5.4) and brain cancer (OR = 1.6, 95% CI 0.7-3.5).[16] Not one of the associations was statistically significant.

Conclusion

- The studies concerning ETS exposure and cancer other than of the lung are few in number and subject to the same criticisms applicable to the lung cancer studies, e.g., "data-dredging," no assessment of exposure, inadequate control for confounding factors. Additionally, there are only one or two reports on a given cancer endpoint. Without replication of the results, it is not possible to reach any conclusion about ETS exposure and non-pulmonary cancer incidence.

2023379951

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Layard, M.W., "Environmental Tobacco Smoke and Cancer: The Epidemiologic Evidence," Environmental Tobacco Smoke: Proceedings of the International Symposium at McGill University 1989, eds. D. Ecobichon and J. Wu, (Lexington, Massachusetts: Lexington Books, 1990): 99-115.

2. Hirayama, T., "Cancer Mortality in Nonsmoking Women with Smoking Husbands Based on a Large-Scale Cohort Study in Japan," Preventive Medicine 13: 680-690, 1984.

3. Miller, G.H., "Cancer, Passive Smoking and Nonemployed and Employed Wives," The Western Journal of Medicine 140: 632-635, 1984.

4. Reynolds, P., Kaplan, G.A. and Cohen, R.D., "Passive Smoking and Cancer Incidence: Prospective Evidence from the Alameda County Study," (abstract) American Journal of Epidemiology 126(4): 767, 1987.

5. Sandler, D.P., Comstock, G.W., Helsing, K.J. and Shore, D.L., "Deaths from All Causes in Non-Smokers Who Lived with Smokers," American Journal of Public Health 79: 163-167, 1989.

6. Holcomb, L.C., "Risk to Passive Smokers," (letter to the editor) American Journal of Public Health 79(10): 1432, 1989.

7. Sandler, D.P., Everson, R.B., Wilcox, A.J. and Browder, J.P., "Cancer Risk in Adulthood from Early Life Exposure to Parents' Smoking," American Journal of Public Health 75(5): 487-492, 1985.

8. Wells, A.J., "Breast Cancer, Cigarette Smoking, and Passive Smoking," (letter to the editor) American Journal of Epidemiology 133(2): 208-210, 1991.

9. Kabat, G.C., Dieck, G.S. and Wynder, E.L., "Bladder Cancer in Nonsmokers," Cancer 57: 362-367, 1986.

10. Burch, J.D., Rohan, T.E., Howe, G.R., Risch, H.A., Hill, G.B., Steele, R. and Miller, A.B., "Risk of Bladder Cancer by Source and Type of Tobacco Exposure: A Case-Control Study," International Journal of Cancer 44: 622-628, 1989.

11. Sandler, D.P., Everson, R.B. and Wilcox, A.J., "Passive Smoking in Adulthood and Cancer Risk," American Journal of Epidemiology 121: 37-48, 1985.

2023279952

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

12. Slattery, M.L., Robison, L.M., Schuman, K.L., French, T.K., Abbott, T.M., Overall, J.C. and Gardner, J.W., "Cigarette Smoking and Exposure to Passive Smoke Are Risk Factors for Cervical Cancer," Journal of the American Medical Association 261: 1593-1598, 1989.

13. Zang, E.A., Wynder, E.L. and Harris, R.E., "Exposure to Cigarette Smoke and Cervical Cancer," (letter to the editor) Journal of the American Medical Association 262(4): 499, 1989.

14. Slattery, M.L., "Exposure to Cigarette Smoke and Cervical Cancer: In Reply," (letter to the editor) Journal of the American Medical Association 262(4): 499, 1989.

15. Grufferman, S., Wang, H.H., DeLong, E.R., Kimm, S.Y.S., Delzell, E.S. and Falletta, J.M., "Environmental Factors in the Etiology of Rhabdomyosarcoma in Childhood," Journal of the National Cancer Institute 68(1): 107-113, 1982.

16. John, E.M., Savitz, D.A. and Sandler, D.P., "Prenatal Exposure to Parents' Smoking and Childhood Cancer," American Journal of Epidemiology 133(2): 123-132, 1991.

2023279953

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023379954

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023373955

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

ETS and Heart Disease

Introduction

This notebook discusses and provides copies of the public literature bearing directly on the claim that environmental tobacco smoke (ETS) is related to heart disease. Most of this literature is epidemiological, with a current total of 11 studies presenting data on a possible statistical association between ETS and heart disease incidence or mortality.

These epidemiological reports are important because they are the primary basis for claims of an elevated heart disease risk in nonsmokers exposed to ETS. However, the literature also contains claims of special harm in compromised individuals, such as heart disease patients, or regarding biochemical effects that might mediate an adverse effect of ETS on heart disease incidence or mortality. Accordingly, this notebook also includes several laboratory and statistical reports dealing with ETS and exercise performance, particularly in angina patients, or with biochemical factors suggested as involved in the development of heart disease.

Each of the articles included in this notebook has been highlighted in blue and yellow. The blue highlighting identifies the most notable comments supporting a relationship of ETS with heart disease, or that are otherwise adverse regarding tobacco or smoking. The yellow highlighting identifies comments that

2023789956

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

challenge, or at least that are concessionary concerning, the potential involvement of ETS or tobacco in disease causation.

The initial section of this notebook contains an overview and discussion of the literature. The literature itself is grouped into four appendices. Appendix A (Tabs 1-13) contains the primary epidemiological reports, consisting of 11 studies reported in 13 articles. A summary and discussion of major criticisms is provided for each individual study. Appendix B (Tabs 14-17) contains the major meta-analyses and reviews concluding that ETS is associated with an elevated heart disease risk. Appendix C (Tabs 18-23) contains the primary reviews which have judged that the data are inadequate to conclude that ETS is related to heart disease. Appendix D (Tabs 24-35) contains a mixed group of articles which provide data concerning ETS in relation to exercise performance, potential effects in heart patients or in relation to cardiovascular biochemical and cellular processes. Short summaries are provided with the articles in Appendix D. If notable letters to the editor or other editorial comments were published concerning any of the articles in this notebook, these materials were also included.

2023279957

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Epidemiologic Reports and Reviews

Reports with original data

There are currently 11 studies (in 13 reports) presenting epidemiological data on a possible statistical association between ETS and heart disease incidence and mortality. There are 13 reports, because for two studies, the data were presented in two separate articles. It should be emphasized, however, that the epidemiological reports on the heart disease issue include several scientifically weak sources, particularly meeting abstracts. Furthermore, all of these studies are open to serious methodological criticisms. Summaries of the individual studies, as well as a list of the major criticisms of each, are provided with the highlighted copies of the articles in Appendix A.

The ETS associated risks reported in the 11 epidemiological studies are summarized in the following table.

2023379958

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

ETS/Heart Disease Epidemiological Reports

	Sex	Reported Risk	Statistical Testing
Butler (1990)[1]	F	RR = 1.40	0.51 - 3.84 (95% CI)
Garland et al. (1985)[2]	F	RR = 2.7	$p \leq .10$
		Ctrl vs. ETS	
Gillis et al. (1984)[3]	M	31 vs 45 per 10^4/yr	No stat. test rpted.
	F	4 vs 12 per 10^4/yr	No stat. test rpted.
*He, et al. (1989)[4]	F	OR = 1.50	$p < .01$
*Helsing, et al. (1988)[5]	M	RR = 1.31	1.1-1.6 (95% CI)
	F	RR = 1.24	1.1-1.4 (95% CI)
Hirayama (1984)[6]	F	RR = 1.31 (husbands smoking $\geq$ 20 cigs/day)	1.06-1.63 (90% CI)
*Hole, et al. (1989)[7]	M+F	RR = 2.01	1.21-3.35 (95% CI)
Humble, et al. (1990)[8]	F	RR = 1.59	0.99-2.57 (95% CI)
Lee, et al. (1986)[9]	M+F	RR = 1.03	0.65-1.62 (95% CI)
*Martin, et al. (1986)[10]	F	RR = 3.4	$p < .01$
Palmer, et al. (1988)[11]	F	RR = 1.2	No stat. test rpted.
*Sandler, et al.(1989)[12]	M	RR = 1.31	1.05-1.64 (95% CI)
	F	RR = 1.19	1.04-1.36 (95% CI)
Svendsen, et al. (1987)[13]	M	RR = 2.23	0.72-6.92 (95% CI)

NOTE: Gillis, et al. (1984) and Hole, et al. (1989) are based on the same study. Also, Helsing, et al. (1988) and Sandler, et al. (1989) are based on the same study.

*Reported to be statistically significant at the 95% level of confidence.

2023279959

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

In an overall evaluation of the epidemiological reports, it is important to consider the issue of statistical significance. Some fluctuation in disease or mortality rates will occur simply by chance alone. Hence, when these rates are compared, as in risk ratios, it is necessary to apply a standard to determine the statistical likelihood that an apparent elevation or reduction in risk reflects chance variation or whether it reflects an actual difference in the comparison groups. The traditional scientific standard is to require that a statistical test indicate at least a 95% probability that an observed difference reflects a true effect. Stated in reverse, this would mean that the standard only allows a 5% probability that the result was due to chance.

When discussing relative risks, if the disease or mortality rates are equivalent in the comparison groups, this will be reflected in a ratio of 1.0. When a statistical test is performed, the 95% standard is met when the 95% confidence intervals are reported not to include 1.0. Sometimes a "p" value is given, which states the probability that an observation is due to chance. Hence, a statement of "p < .05" means that the observation could have occurred by chance less than 5% of the time. To state "p < .05" or to provide 95% confidence intervals that do not include 1.0, are equivalent indications of statistical significance.

2023799960

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Only four of the 11 epidemiological studies regarding ETS and heart disease report a statistically significant result at the 95% level of confidence. (1) He, et al. (1989), a Chinese language report based on only 34 female heart disease patients; (2) Helsing, et al. (1988)/Sandler, et al. (1989), a study based on a Maryland census in which the information regarding spousal smoking (used to estimate ETS exposure) was from 1963; (3) Hole, et al. (1989), a Scottish study based on only 84 heart disease deaths; and (4) Martin, et al. (1988), a report based on 23 women who reported having a heart attack and which was given a conference but apparently not otherwise accepted for publication.

In sum, seven of the 11 studies of ETS exposure and heart disease have failed to report a statistically significant association. In the four studies that have claimed a statistically significant relationship, two were from outside the United States. Three were very small-scale. All of these studies suffer from a variety of serious methodological weaknesses.

A list of the most common weaknesses in the individual studies is provided below. It will be recognized that these are characteristic of epidemiological studies of ETS in general, not simply those relating to heart disease. For a more detailed discussion of the criticisms applicable to each study, see Appendix A.

2023273961

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

1. Small sample sizes.

2. Lack of statistical significance, or failure to test for statistical significance.

3. Potential misclassification of the smoking status of study participants.

4. Inadequate assessment of ETS exposure.

5. Failure to control adequately for biases stemming from potential confounding variables.

6. Failure to confirm causes of death via autopsy or other histological methods.

Reviews claiming ETS-associated risk

Despite the scientific weaknesses in the epidemiologic literature on ETS and heart disease, four recent reviews have concluded that ETS is associated with an increased risk of heart disease and that, in fact, such exposure causes a large number of deaths each year. Copies of these reviews are provided in Appendix B. Each of these reviews attempted to estimate an overall risk based on the combined data from the epidemiologic studies. These estimated risk ratios and the associated 95% confidence intervals are provided in the following table.

2023379962

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Meta-Analyses and Reviews of ETS-Heart Disease Data

		RR	95% CI
Wells (1988)[14]	Males	1.31	(1.1-1.6)
	Females	1.23	(1.11-1.36)
	Home		
Kawachi, et al. (1989)[15]	Males	1.3	(1.1-1.6)
	Females	1.2	(1.1-1.4)
	Workplace		
	Males	2.3	(1.4-3.4)
	Females	1.9	(1.4-2.5)
Kristensen (1989)[16]	Both sexes	≈ 1.3	
Glantz and Parmley (1991)[17]	Both sexes	1.3	(1.2-1.4)

These estimates were generally derived from the statistical technique known as meta-analysis. (The Kristensen article appears to be an exception, in that the estimated 1.3 relative risk was apparently based on an informal estimation and no confidence intervals were given.) Although these reviews varied somewhat in form, detail and focus, the estimates were generally similar, about 1.3, reflecting a 30% elevation in risk associated with ETS exposure.

The Kawachi, et al. (1989) discussion was fairly narrowly focused on New Zealand. The Kristensen (1989) discussion was a

2023379963

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

limited part of a larger discussion of factors involved in cardiovascular diseases and the work environment. Thus, the major reviews, both of which clearly involved meta-analytic techniques, were those by Wells in 1988 and by Glantz and Parmley in 1991. These two reports are discussed further below.

A. Judson Wells, a consultant to the American Lung Association, statistically combined the data from several reports on ETS and heart disease, including both prospective (cohort) and case-control studies. He then calculated overall relative risks (ETS exposed versus nonexposed) for lung cancer (1.44 for females; 2.1 for males), cancers other than lung (1.16 for females; no risk elevation for males) and heart disease (1.23 for females; 1.31 for males). He also estimated numbers of death related to these disease categories, claiming that ETS exposure results in 46,000 deaths per year in nonsmokers. Of these, 3,000 are claimed to be from lung cancer. For cancers other than the lung, he calculated that ETS exposure results in 11,000 annual deaths. The largest number of deaths from ETS exposure was claimed to be due to heart disease. He claimed that 32,000 nonsmoker heart disease deaths per year stem from ETS exposure.

The most recent, and certainly the most widely publicized, review of ETS and heart disease was undertaken by two authors from the Department of Medicine, University of California, San Francisco.

2023379964

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

In their 1991 paper, Stanton Glantz and William Parmley conclude that ETS exposure is statistically associated with an estimated 30% increase (relative risk of 1.3) in heart disease risk in nonsmokers. They argue that this translates into 37,000 heart disease deaths in nonsmokers stemming from ETS exposure. Glantz and Parmley also discuss a number of biochemical and experimental studies which purportedly support the biological plausibility of such a relationship.

In evaluating the claims by Wells and by Glantz and Parmley, it should be emphasized that meta-analysis, the technique from which they derive their risk estimates, is appropriately used only when the underlying studies are highly similar and of high quality. If the underlying studies are based on different populations and procedures and suffer from serious methodological weaknesses, then any meta-analysis will consequently be invalidated.

The above considerations are directly applicable to an evaluation of the risk claims regarding ETS and heart disease. These claims are based on meta-analyses of a small group of epidemiological studies reporting a relationship between ETS exposure and an increased risk of heart disease. In general, these studies deal with spousal smoking and assess heart disease risk in the nonsmoking spouse. Otherwise, these studies used widely disparate methodologies, study populations and endpoints. Several

2023379965

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

are very weak, preliminary, available only in abstract form, or are based on such scanty data that they quite arguably are not sufficiently reliable or valid even to be considered seriously in a meta-analysis. Appendix A contains discussions of the major flaws in the individual studies.

Reviews emphazing inconclusiveness of the data

Reviews such as those by Wells and by Glantz and Parmley often receive a great deal of publicity. However, it is important to recognize that there have been a number of other examinations of the data concerning ETS and heart disease. Several important reviews have concluded that the data on this issue are equivocal and inadequate to support claims of an increased heart disease risk in nonsmokers exposed to ETS.

The first major reviews of the epidemiological data on ETS and heart disease appeared in 1986. In that year, a report of the United States Surgeon General[18] examined the available data and judged that "no firm conclusion" (p. 10) could be made regarding a possible relationship between ETS and heart disease. Also in 1986, a similar evaluation appeared from a committee of the National Research Council of the National Academy of Sciences.[19] This committee calculated that any potential heart disease risk related to ETS would be "difficult to detect or estimate reliably" from

2023279966

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

epidemiological studies, and would be "the same order of magnitude as what might arise from expected residual confounding due to unmeasured covariates." (p. 263)

Thus, both the 1986 Surgeon General's Report and the National Research Council report judged that the data were insufficient to allow a conclusion that ETS exposure is a cause of heart disease. Even the 1991 review by Glantz and Parmley recognized this as a "reasonable" position, at least in 1986. On the other hand, Glantz and Parmley argued that data published since 1986 warrant that this conclusion be modified. However, other scientists have undertaken more balanced and critical reviews of the more recent data and have judged that it remains inconclusive. The four most significant of these reviews, and their conclusions, are as follows:

a. At a major conference on ETS held at McGill University in 1989, Lawrence Wexler, of the New York Medical College, concluded that recent data did not provide a basis for altering the earlier conclusions by the Surgeon General and National Research Council concerning ETS and cardiovascular disease.

> Based on the available evidence, it is this author's opinion that it has not been demonstrated that exposure to ETS increases the risk of cardiovascular disease. (p. 139)[20]

2023379967

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

b. A similar evaluation was made by two scientists from the United Kingdom, who reviewed the literature on ETS and heart disease and presented their conclusions at an international conference on indoor air quality held in Lisbon, Portugal in April 1990.

> It is concluded that no increased risk of cardiovascular disease can be associated unequivocally with exposure to ETS, and it seems probable that this will continue to be the case until specifically designed trials are instigated, and some objective measure of degree of exposure can be devised. (p. 215)[21]

c. Another scientific review of this literature was performed by two physicians from the University of Munich, Germany and given at an international conference in Hungary in June 1990. The conclusion was similar.

> Taking into account the small increase in coronary risk in passive smokers as compared to non-exposed subjects and also the low validity and small number of epidemiological studies available and the fact that their results are at least inconsistent, a relationship between passive smoking and cardiovascular diseases cannot be established on these data. (p. 6)[22]

d. In a 1991 book discussing a wide range of issues involving ETS, the literature on heart disease was reviewed by Alan Armitage, former director of toxicology of a major European research laboratory and now head of pharmacology at

2023379968

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

the Tobacco Research Council Laboratories in the United Kingdom. He judged that the scientific data have not established an increased heart disease risk in nonsmokers exposed to ETS.

> It is clear that the evidence for a harmful effect of ETS in enhancing CHD [coronary heart disease] risk in non-smokers is not very convincing. . . . (p. 114)[23]

Studies Involving Exercise Performance, Heart Disease Patients and Biochemical Measurements

There are several experimental and biochemical studies that have been cited in the literature as supporting an increase in heart disease risk stemming from ETS exposure. A few of these reports claim that ETS exposure adversely effects exercise capacity and that in the case of heart disease patients, this can lead to attacks of angina (heart pain). Other reports have attempted to demonstrate that ETS exposure adversely affects some aspect of cardiovascular function, such as blood clotting (platelets), myocardial respiration (oxygen usage) or cholestol levels. These articles, with brief summaries, are provided in Appendix D.

In an overall evaluation of these studies, it is important to note that they constitute a relatively minor aspect of the ETS/heart disease issue. That is, the claim that ETS increases the risk of heart disease is a statistical statement based on epidemiological reports. Once having made that statement, various

2023379969

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

kinds of studies dealing with cardiovascular or exercise performance or with mechanisms might be marshalled to argue for its plausibility. On the other hand, without the epidemiological underpinning, such studies would probably be much less notable since there would be nothing that they would be attempting to explain.

In the area of exercise performance, there are three primary studies. In one of these, a 1985 report by McMurray, et al.,[24] healthy subjects were used and ETS exposure was claimed to have an adverse effect on exercise performance. Two other studies, one by Aronow (1978)[25] and the other by Khalfen and Klochkov (1987)[26] used angina patients. In somewhat similar study designs, both reports claimed that when these heart disease patients were exposed to ETS, they were not able to exercise as long before experiencing angina. The credibility of the Aronow report has been widely challenged in the literature. The Khalfen and Klochkov report is a Russian language article about which relatively little is known. Regarding any of the exercise performance studies, whether with healthy or heart disease patients, a general criticism is that when dealing with ETS, it is almost impossible to "blind" either the experimenter or the subjects with regard to ETS exposure. Thus, the possibility is always open that some subjective factor may influence the results.

2023279970

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

There are very limited data attempting to demonstrate that ETS adversely affects some process that might be involved in blood clotting (thrombus formation) or atherosclerosis. The primary focus has been on the possibility that ETS may increase the tendency of certain blood components, known as platelets, to stick together. This claim has been made based mainly on data in four published reports. Three of these are from the same Austrian research group. (Sinzinger and Kefalides, 1982[27]; Burghuber, et al., 1986[28]; Sinzinger and Virgolini, 1989[29]) Of these three, one is merely a letter to the editor (Sinzinger and Kefalides, 1982) and another is a German language article with only an English abstract (Sinzinger and Virgolini, 1989). The fourth report, Davis, et al., (1989)[30] is from a group of researchers in Kansas City, Missouri. It suffers from serious methodological weaknesses, particularly its failure to establish a proper control condition.

Finally, there are two reports of children which assessed cholesterol and other blood components in relation to parental smoking status (Moskowitz, et al., 1990[31]; Pomrehn, et al., 1990[32]), one of which (Pomrehn, et al., 1990) is only available as an abstract from a meeting presentation. Both reports claimed that parental smoking was associated with decreases in HDL cholesterol, which some literature has argued may be associated with heart disease risk. These studies measured components of blood as the endpoint, but are essentially epidemiological studies in that they,

2023279971

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

at best, may suggest statistical correlations. As such, they suffer from weaknesses characteristic of other epidemiological studies of ETS exposure, especially difficulties in controlling for potential confounding variables and inadequate assessment of ETS exposure. Furthermore, the potential significance of blood values in relation to later heart disease risk in a group of children is highly speculative.

This notebook also contains a group of three articles relating to research from a Czechoslovakian group, which claims that "passive smoking" has an adverse effect on the heart's use of oxygen.[33 34 35] These were animal studies involving smoke exposure to rabbits. They clearly involved a design intended to mimic "active" smoking, and are included in this notebook merely because they were erroneously discussed in the 1991 Glantz and Parmley paper as providing data relevant to ETS exposure.

WLS/tks

2023279922

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Endnotes

1. Butler, T., "The Relationship of Passive Smoking to Various Health Outcomes Among Seventh-Day Adventists in California," Presented at the Seventh World Conference on Tobacco and Health, Abstract, 1990.

2. Garland, C., Barrett-Connor, E., Suarez, L., Criqui, M.H. and Wingard, D.L., "Effects of Passive Smoking on Ischemic Heart Disease Mortality of Nonsmokers: A Prospective Study," American Journal of Epidemiology 121(5): 645-650, 1985.

   Garland, C., Barrett-Connor, E., Suarez, L., Criqui, M.H. and Wingard, D.L., "Effects of Passive Smoking on Ischemic Heart Disease Mortality of Nonsmokers: A Prospective Study," Erratum, American Journal of Epidemiology 122: 1112, 1985.

3. Gillis, C.R., Hole, D.J., Hawthorne, V.M. and Boyle, P., "The Effect of Environmental Tobacco Smoke in Two Urban Communities in the West of Scotland." In: ETS - Environmental Tobacco Smoke: Report from a Workshop on Effects and Exposure Levels. R. Rylander, Y. Peterson and M.C. Snella (eds.). European Journal of Respiratory Diseases, Supplement No. 133, Vol. 65, 121-126, 1984.

4. He, Y., et al., "Women's Passive Smoking and Coronary Heart Disease," Chung Hua Yu Fang I Hsuch Tsa Chih 23(1): 19-22, 1989.

5. Helsing, K.J., Sandler, D.P., Comstock, G.W. and Chee, E., "Heart Disease Mortality in Nonsmokers Living With Smokers," American Journal of Epidemiology 127(5): 915-922, 1988.

6. Hirayama, T., "Lung Cancer in Japan: Effects of Nutrition and Passive Smoking." In: Lung Cancer: Causes and Prevention. M. Mizell and P. Correa (eds.). New York, Verlag Chemie International, Chapter 14, 175-195, 1984.

7. Hole, D.J., Gillis, C.R., Chopra, C. and Hawthorne, V.M., "Passive Smoking and Cardiorespiratory Health in a General Population in the West of Scotland," British Medical Journal 299: 423-427, 1989.

8. Humble, C., Croft, J., Gerber, A., Casper, M., Hames, C.G. and Tyroler, H.A., "Passive Smoking and 20-Year Cardiovascular Disease Mortality among Nonsmoking Wives, Evans County, Georgia," American Journal of Public Health 80(5): 599-601, 1990.

10381016

2023379973

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

9. Lee, P.N., Chamberlain, J. and Alderson, M.R., "Relationship of Passive Smoking to Risk of Lung Cancer and Other Smoking-Associated Diseases," British Journal of Cancer 54: 97-105, 1986.

10. Martin, M.J., Hunt, S.C. and Williams, R.R., "Increased Incidence of Heart Attacks in Nonsmoking Women Married to Smokers," Presented at the Annual Meeting of the American Public Health Association, Abstract, 1986.

11. Palmer, J.R., Rosenberg, L. and Shapiro, S., "Passive Smoking and Myocardial Infarction in Women," Abstract, CVD Epidemiology Newsletter No. 43, 29, Winter 1988.

12. Sandler, D.P., Comstock, G.W., Helsing, K.J. and Shore, D.L., "Deaths from All Causes in Non-Smokers Who Lived with Smokers," American Journal of Public Health 79(2): 163-167, 1989.

13. Svendsen, K.H., Kuller, L.H., Martin, M.J. and Ockene, J.K., "Effects of Passive Smoking in the Multiple Risk Factor Intervention Trial," American Journal of Epidemiology 126(5): 783-795, 1987.

14. Wells, A.J., "An Estimate of Adult Mortality in the United States from Passive Smoking," Environment International 14(3): 249-265, 1988.

15. Kawachi, I., Pearce, N.E. and Jackson, R.T., "Deaths from Lung Cancer and Ischaemic Heart Disease Due to Passive Smoking in New Zealand," New Zealand Medical Journal 102(871): 337-340, 1989.

16. Kristensen, T.S., "Cardiovascular Diseases and the Work Environment. A Critical Review of the Epidemiologic Literature on Chemical Factors," Scand. J. Work Environ. Health 15: 245-264, 1989.

17. Glantz, S.A. and Parmley, W.W., "Passive Smoking and Heart Disease: Epidemiology, Physiology, and Biochemistry," Circulation 83(1): 1-12, 1991.

18. U.S. Department of Health and Human Services, The Health Consequences of Involuntary Smoking: A Report of the Surgeon General. Publication No. DHHS (CDC) 87-8398, Washington, D.C., U.S. Government Printing Office, 1986.

19. Committee on Passive Smoking, Board on Environmental Studies and Toxicology, National Research Council, National Academy of Sciences, Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects. Washington, D.C., National

2023379274

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Academy Press, 1986.

20. Wexler, L.M., "Environmental Tobacco Smoke and Cardiovascular Disease: A Critique of the Epidemiological Literature and Recommendations for Future Research." In: Environmental Tobacco Smoke: Proceedings of the International Symposium at McGill University 1989. D.J. Ecobichon and J.M. Wu (eds.). Lexington, Mass., Lexington Books, D.C. Heath and Company, Chapter 8, 139-152, 1990.

21. Weetman, D.F. and Munby, J., "Environmental Tobacco Smoke (ETS) and Cardiovascular Disease." In: Indoor Air Quality and Ventilation. F. Lunau and G.L. Reynolds (eds.). London, Selper Ltd., 211-216, 1990.

22. Thiery, J. and Cremer, P., "Coronary Heart Disease and Involuntary Smoking," Paper presented at: Toxicology Forum (Session on "Environmental Tobacco Smoke: Science and Meta-Science"), Budapest, Hungary, June 19, 1990.

23. Armitage, A.K., "Environmental Tobacco Smoke and Coronary Heart Disease." In: Other People's Tobacco Smoke. A.K. Armitage (ed.). Beverly, E. Yorks, U.K., Galen Press, Chapter 7, 109-116, 1991.

24. McMurray, R.G., Hicks, L.L. and Thompson, D.L., "The Effects of Passive Inhalation of Cigarette Smoke on Exercise Performance," European Journal of Applied Physiology 54(2): 196-200, 1985.

25. Aronow, W.S., "Effect of Passive Smoking on Angina Pectoris," New England Journal of Medicine 299(1): 21-24, 1978.

26. Khalfen, E.Sh. and Klochkov, V.A., "Effect of 'Passive' Smoking on the Physical Load Tolerance of Coronary Heart Disease Patients," Ter. Arkh. 5: 112-115, 1987. [Uncertified translation]

27. Sinzinger, H. and Kefalides, A., "Passive Smoking Severely Decreases Platelet Sensitivity to Antiaggregatory Prostaglandins," Letter, The Lancet II, pp. 392-393, August 14, 1982.

28. Burghuber, O.C., Punzengruber, Ch., Sinzinger, H., Haber, P. and Silberbauer, K., "Platelet Sensitivity to Prostacyclin in Smokers and Non-smokers," Chest 90(1): 34-38, 1986.

29. Sinzinger, H. and Virgolini, I., "Are Passive Smokers at Greater Risk of Thrombosis?" Wiener Klinische Wochenschrift 20: 649-698, 1989.

10381016

2023379975

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

30. Davis, J.W., Shelton, L., Watanabe, I.S. and Arnold, J., "Passive Smoking Affects Endothelium and Platelets," Arach. Intern. Med. 149: 386-389, 1989.

31. Moskowitz, W.B., Mosteller, M., Schiekern, R.M., Bossano, R., Hewitt, J.K., Bodurtha, J.N. and Segrest, J.P., "Lipoprotein and Oxygen Transport Alterations in Passive Smoking Preadolescent Children: The MCV Twin Study," Circulation 81(2): 586-592, 1990.

32. Pomrehn, P., Hollarbush, J., Clarke, W. and Lauer, R., "Children's HDL--chol: The Effects of Tobacco; Smoking, Smokeless and Parental Smoking," Presented at the 30th Annual Conference on Cardiovascular Disease Epidemiology, Abstract, Circulation 81(2): 720, 1990.

33. Gvozdjakova, A., Bada, V., Sany, L., Kucharska, J., Kruty, F., Bozek, P. Trstansky, L. and Gvozdjak, J., "Smoke Cardiomyopathy: Disturbance of Oxidative Processes in Myocardial Mitochondria," Cardiovascular Research 18: 229-232, 1984.

34. Gvozdjakova, A., Kucharska, J., Sany, L., Bada, V., Bozek, P. and Gvozdjak, T., "Effect of Smoking on the Cytochrome and Oxidase System of the Myocardium," Bratisl. lek. Listy 83: 10-15, 1985.

35. Gvozdjak, J., Gvozdjakova, A., Kucharska, J. and Bada, V., "The Effect of Smoking on Myocardial Metabolism," Czech. Med. 10(1): 47-53, 1987.

2023279976

10381016

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

ETS/RD & CONDITIONS
IN NONSMK ADLTS & CH

2023379977

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

20233799978

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

PARENTAL SMOKING AND CHILDHOOD RESPIRATORY DISEASE/SYMPTOMS

2023279979

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

PARENTAL SMOKING

Perhaps no claim regarding environmental tobacco smoke (ETS) is as capable of provoking strong feelings as the charge that parents who smoke may compromise the health of their children. While the issue of parental smoking is laden with emotion, the scientific basis for the claim is difficult to interpret. None of the studies that have reported an association between parental smoking and a child's increased risk of developing respiratory infections or symptoms have actually measured exposure to ETS. Virtually all of the studies have failed to control for cross-infections in the home and other important confounding factors. Studies that have controlled for such factors have frequently reported no significant increased risk of respiratory disease in the children of smoking parents.[1-17]

The studies on parental smoking, each with a different sample size, data collection method and analysis, tend to yield factually incompatible and contrary conclusions. For instance, although certain studies and reviews have reported adverse findings,[18-42] others have observed no significant relationship between parental smoking and respiratory illness in children.[5,6,8,43-53] After a five-year study of over 400 children, for example, Dutch researchers concluded there was "no evidence" that parental smoking had an appreciable effect on respiratory symptoms in school children.[49] A similar conclusion was reached by a group of U.S. researchers, including a critic of smoking, who found "no significant relation" between parental smoking and

2023273980

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

respiratory symptoms in a study of nearly 400 families with 816 children in three cities.[43]

In 1988, investigators re-examined thirty studies on ETS exposures among children and evaluated the studies for their scientific validity.[54] They noted that while several studies had reported a statistically significant relationship between ETS exposure and respiratory illness in children, "most studies had significant design problems that prevent reliance on their conclusions." The authors concluded that "many questions remain, and future studies should consider important methodological standards to determine more accurately the effect of passive smoking on child health." In 1990, another group of researchers examined the existing literature on ETS and respiratory health.[55] Although critical of ETS, they concluded that "[f]urther studies of health effects are needed; such studies will require improved methods of exposure assessment, as well as better understanding of dose-response relationships."

The studies on parental smoking have relied solely on questionnaires to obtain exposure data.[55] Reliance on questionnaires casts doubt on the findings of these studies for several reasons. First, it has been noted that even "slight changes" in the way the questions were phrased could result "in substantial differences in the type of responses one obtains."[28] Secondly, one study observed that there was a significant difference in the respiratory symptoms reported depending on which

2023273981

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

parent completed the questionnaire.[38] It has been reported that mothers are more likely than fathers to report chronic respiratory problems in their children and that asymptomatic mothers are less likely than symptomatic mothers to report symptoms in their children.[55] It has been suggested that "[t]hese potential biases must be evaluated in epidemiologic studies."[55]

In conclusion, although a number of studies have been conducted on parental smoking and childhood respiratory health, the results of these studies are inconsistent and are limited by the methodology employed in each study. Questionnaires are not an accurate method of determining the actual exposure of ETS a child receives from his/her smoking parent. Many studies report no relationship for parental smoking, particularly when confounding factors such as diet, home dampness or cross-infection in and outside the home are considered. Childhood respiratory illness appears to be influenced by many different social, familial, and environmental factors. To isolate parental smoking as a cause is scientifically unjustified.

2023379982

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Anderson, L., et al., "Day Care Center Attendance and Hospitalization for Lower Respiratory Tract Illness," Pediatrics 82(3): 300-308, 1988.

2. Berwick, M., et al., "Lower Respiratory Symptoms in Children Exposed to Nitrogen Dioxide From Unvented Combustion Sources," Environment International 15: 369-373, 1989.

3. Berglund, B., et al., "Radon, Passive Smoking, Particulates and Housing Epidemiology," Indoor Air 2: 255-260, 1984.

4. Brunekreef, B., et al., "Home Dampness and Respiratory Morbidity in Children," Am. Rev. Respir. Dis 140: 1363-1367, 1989.

5. Harrington, W. and Krupnick, Alan J., "Short-Term Nitrogen Dioxide Exposure and Acute Respiratory Disease in Children," JAPCA 35: 1061-1087, 1985.

6. Holma, B. and Winding, O., "Housing, Hygiene, and Health: A Study in Old Residential Areas in Copenhagen," Archives of Environmental Health 32(2): 86-93, 1977.

7. Kerigan, A., et al., "A Three-Year Cohort Study of the Role of Environmental Factors in the Respiratory Health of Children

2023379983

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

in Hamilton, Ontario," Am. Rev. Respir. Dis. 133: 987-993, 1986.

8. Martin, C., et al., "Housing Conditions and Ill Health," British Medical Journal 294: 1987.

9. Melia, R.J.W., et al., "Association Between Gas Cooking and Respiratory Disease in Children," British Medical Journal, 149-152, 1977.

10. Melia, R.J.W., et al., "The Relation Between Respiratory Illness in Primary Schoolchildren and the Use of Gas for Cooking, I- Results From a National Survey," International Journal of Epidemiology 8(4): 333-338, 1979.

11. National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, May 1-3, 1983, "Report of Workshop on Respiratory Effects of Involuntary Smoke Exposure: Epidemiologic Studies"

12. Mitchell, E., et al., "Socioeconomic Status in Childhood Asthma," International Journal of Epidemiology 18(4): 888-890, 1989.

13. Nordvall, S.L., et al., "Sensitization of Children in the Stockholm Area to House Dust Mites," Acta Paediatr Scan 77(5): 716-720, 1988.

2023279984

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

14. Osborne, J.S., "Health Effects of Heating With Wood: Chest Illness in Young Children and Indoor Heating with Woodburning Stoves," The Human Equation: Health and Comfort, Indoor Air Quality '89, April 17-20, 1989, San Diego, CA.

15. Platt, S., et al., "Damp Housing, Mould Growth, and Symptomatic Health State," BMJ 298: 1673-1678, 1989.

16. Pope, C., "Respiratory Disease Associated with Community Air Pollution and a Steel Mill, Utah Valley," AJPH 79(5): 623-628, 1989.

17. Strachan, D. and Elton, R., "Relationship Between Respiratory Morbidity in Children and the Home Environment," Family Practice 3(3): 137-142, 1986.

18. Committee on Passive Smoking, Board on Environmental Studies and Toxicology, National Research Council, Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects (Washington: National Academy Press, 1986).

19. U.S. Department of Health and Human Services, The Health Consequences of Involuntary Smoking: A Report of the Surgeon General (U.S. DHHS: Washington, 1986).

2023373985

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

20. Bland, M., et al., "Effect of Children's and Parents' Smoking on Respiratory Symptoms," Arch Dis Child 53(2): 100-105, 1978.

21. Bonham, G. and R. Wilson, "Children's Health in Families with Cigarette Smokers," Am Public Health 71(3): 290-293, 1981.

22. Burchfiel, C., et al., "Passive Smoking in Childhood: Respiratory Conditions and Pulmonary Function in Tecumseh, Michigan," Am Rev Respir Dis 133(6): 966-73, 1986.

23. Cameron, P. and D. Robertson, "Effect on Home Environment Tobacco Smoke on Family Health," J Appl Psychol 57(2): 142-147, 1973.

24. Chen, Y., "Synergistic Effect of Passive Smoking and Artificial Feeding on Hospitalization for Respiratory Illness in Early Childhood," Chest 95: 1004-07, 1989.

25. Colley, J., "Respiratory Symptoms in Children and Parental Smoking and Phlegm Production," Br Med J II: 201-204, 1974.

26. Colley, J., et al., "Influence of Passive Smoking and Parental Phlegm on Pneumonia and Bronchitis in Early Childhood," Lancet II: 1031-1034, 1974.

2023373386

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

27. Dockery, D., et al., "Effects of Inhalable Particles on Respiratory Health of Children," Am Rev Respir Dis 139: 587-594, 1989.

28. Ekwo, E., et al., "Relationship of Parental Smoking and Gas Cooking to Respiratory Disease in Children," Chest 84(6): 662-668, 1983.

29. Fergusson, D., et al., "Parental Smoking and Lower Respiratory Illness in the First Three Years of Life," J Epidemiol Community Health 35(3): 180-184, 1981.

30. Fergusson, D., et al., "Parental Smoking and Respiratory Illness During Early Childhood," Ped Pul 1(2): 99-106, 1985.

31. Ferris, B., et al., "The Six-City Study: Examples of Problems in Analysis of Data," Environ Health Perspect 52: 115-123, 1983.

32. Gortmaker, S., et al., "Parental Smoking and the Risk of Childhood Asthma," Am J Public Health 72(6): 574-579, 1982.

33. Harlap, S. and A. Davies, "Infant Admissions to Hospital and Maternal Smoking," Lancet I: 529-532, 1974.

2023739387

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

34. Kraemer, M., et al., "Risk Factors for Persistent middle Ear Effusions: Otitis Media, Catarrh, Cigarette Smoke Exposure, and Atopy," JAMA 249(8): 1022-1025, 1983.

35. Murray, A., and B. Morrison, "Passive Smoking and the Seasonal Difference of Severity of Asthma in Children," Chest 94(4): 701-708, 1988.

36. Neuspiel, D., et al., "Parental Smoking and Post-Infancy Wheezing in Children: A Prospective Cohort Study," AJPH 79(2): 168-171, 1989.

37. Ogston, S., et al., "Association of Infant Alimentary and Respiratory Illness with Parental Smoking and Other Environmental Factors," J Epidemiol Commun Health 41(1): 21-25, 1987.

38. Schenker, M., et al., "Risk Factors for Childhood Respiratory Disease: The Effect of Host Factors and Home Environmental Exposures," Am Rev Respir Dis 128: 1038-1043, 1983.

39. Somerville, S., et al., "Passive Smoking and Respiratory Conditions in Primary School Children," J Epidemiol Commun Health 42(2): 105-110, 1988.

2023379388

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

40. Strachan, D., et al., "Passive Smoking, Salivary Cotinine Concentrations, and Middle Ear Effusion in 7 Year Old Children," BMJ 298: 1549-1552, 1989.

41. Tsimoyianis, G., et al., "Reduction in Pulmonary Function and Increased Frequency of Cough Associated With Passive Smoking in Teenage Athletes," Pediatrics 80(1): 32-36, 1987.

42. Ware, J., et al., "Passive Smoking, Gas Cooking, and Respiratory Health of Children Living in Six Cities," Am Rev Respir Dis 129: 366-374, 1984.

43. Schilling, R., et al., "Lung Function, Respiratory Disease, and Smoking in Families," Am J Epidemiol 106(4): 274-283, 1977.

44. Camacho, E., et al., "Pulmonary Symptoms and Pulmonary Functional Tests Among Children in Relation to the Area of Residence," Eur Respir Dis 63(2): 165-166, 1982.

45. Binder, R., et al., "Importance of the Indoor Environment in Air Pollution Exposure," Arch Environ Health 31(6): 277-279, 1976.

46. Bouhuys, A., "Lung Diseases in Rural and Urban Communities," Report Sponsored by the Division of Lung Diseases, National

2023379389

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Heart, Lung and Blood Institute, U.S. National Institutes of Health, pp. 77-89, June 10, 1977.

47. Gardner, G., et al., "Effects of Social and Family Factors on Viral Respiratory Infection and Illness in the First Year of Life," J Epidemiol Community Health 38: 42-48, 1984.

48. Kallail, K., et al., "Passive Smoking and Middle Ear Problems in Kansas Public School Children," J Commun Disord 20: 187-96, 1987.

49. Kerrebijn, J., et al., "Chronic Nonspecific Respiratory Disease in Children, A Five Year Follow-Up Study," Acta Paediatr Scand, Suppl. 261: 11-72, 1977.

50. Lebowitz, M. and B. Burrows, "Respiratory Symptoms Related to Smoking Habits of Family Adults," Chest 69(1): 48-50, 1976.

51. Love, G., et al., "The Incidence and Severity of Acute Respiratory Illness in Families Exposed to Different Levels of Air Pollution, New York Metropolitan Area, 1971-72," Arch Environ Health 36(2): 66-73, 1981.

52. Salzman, M., et al., "Passive Smoking and Croup," Arch Otolaryngol Head Neck Surg 113: 866-868, 1987.

2023379990

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

53. Shy, C., et al., "The Chattanooga School Children Study: Effects of Community Exposure to Nitrogen Dioxide. II. Incidence of Acute Respiratory Illness," J Air Pollut Control Assoc 20(9): 582-588, 1970.

54. Rubin, D. and K. Damus, "The Relationship Between Passive Smoking and Child Health: Methodologic Criteria Applied to Prior Studies," Yale J Bio Med 61(5): 401-411, 1988.

55. Schenker, M.B. and Pocekay, D.E., "Environmental Tobaco Smoke: Assessment of Exposure and Effects on Respiratory Health" Problems in Resp. Care 3(2): 193-205, 1990.

2023279391

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

14

2023278392

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

PARENTAL SMOKING AND CHILDRENS' LUNG FUNCTION

2023379993

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

LUNG FUNCTION IN CHILDREN

The studies that have investigated lung function in children and its possible relationship to environmental tobacco smoke exposure are presented in this section. To aid in the interpretation of this literature, definitions of the major lung function parameters are provided below.

Df: One of the most widely used measures of pulmonary function in adults and children is forced vital capacity and is represented in the literature as FVC. This term refers to the maximum volume of gas that a person can expire as forcefully and rapidly as possible from their lungs immediately following a maximal inspiration of air. When a person's ability to expire air forcefully and rapidly from their lungs (FVC) is compromised, this can possibly be an indication of chronic obstructive lung disease. Decreased FVC is common in restrictive diseases such as pulmonary fibrosis and in obstructive diseases such as emphysema and asthma.

Df: A second important measure of pulmonary function is the forced expiratory volume in one second, which is abbreviated as FEV1 in the literature. The FEV1 measure is simply the amount of air that is expired in the first second of the FVC maneuver. As with FVC, this parameter is useful in the assessment of airway obstruction. The two parameters, FVC and FEV1, are often used in a ratio to determine the percentage of a person's FVC that is expired in the first second of the maneuver. A FEV1/FVC ratio lower than 65% to 70% is characteristic of obstructive lung disease. On the other hand, subjects with restrictive lung disease will often show a normal or exaggerated FEV1/FVC value.

Df: Forced expiratory flow, known as FEF25%-75%, is the average rate of flow of air during the middle half of an FEV maneuver. The FEF25%-75% is indicative of the status of the medium and small sized airways. Decreased values of FEF25%-75% are common in the early stages of obstructive lung disease. Low values of FEF25%-75% in combination with normal values of FVC and FEV1 are often indicative of early small airways abnormality. Reduced FEF25%-75% are sometimes seen in cases of severe restrictive disease as well.

All of these measures share a common problem: accurate assessment requires the full cooperation and maximal effort of the subjects under investigation. Accurate measures are sometimes

2023375994

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

therefore difficult to obtain, especially when the subjects are young children who do not fully comprehend the requirements being made of them in the pulmonary function tests. The studies are not consistent in the lung function parameters they measure, and there is also a lack of consistency among the results of the same function tests across studies. Following is a presentation of the major studies that have examined these lung function parameters in children. The investigators who have found associations between impaired lung function and ETS exposure are often uncertain of the clinical meanings of the small decreases observed in their studies. Therefore, it is not suprising that no definitive conclusions have been reached regarding ETS exposure and its possible association with lung function in children.

2023379395

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCE

Ruppel, Gregg. Manual of pulmonary function testing (Fourth edition). The C.V. Mosby Company, 1986, pp. 33-38.

2023279396

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

RESULTS OF SELECTED STUDIES: CHILDHOOD LUNG FUNCTION

STUDY	EFFECT ON FEV1, FEV.75	EFFECT ON FEF25-75%
Tager 1976	decrease	not reported
Tager 1979	none	decrease
Weiss 1980	none	decrease
Tager 1983	decrease 7%	none
O'Connor 1987	decrease 5-7%	decrease 14-15%
Ware 1984	decrease .6-.9%	not reported
Berkey 1986	decrease .85%	not reported
Hasselblad 1981	decrease .5-2%	not reported
Tashkin 1984	none	decrease 2.5%
Ekwo 1983	none	none
Vedal 1984	none	decrease 4%
Spinaci 1985	decrease	none
Chen 1986	decrease 3%	decrease 6%
Burchfiel 1986	decrease 4-5%	not reported
Yarnell 1979	decrease 3%	decrease 12%
Teculesco 1986	decrease 5%	not reported
Tsimoyianis 1987	not done	decrease
Lebowitz 1987	none	not done
Leeder 1976	not done	not done
Schilling 1977	none	not reported
Speizer 1980	none	not reported
Dodge 1982	none	not reported
Lebowitz 1984	none	not reported
Lebowitz 1984	not done	not done

Adapted from Witorsch 1989

2023379997

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023373398

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

PARENTAL SMOKING AND COMPROMISED CHILDREN

2023373999

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

COMPROMISED CHILDREN

The literature on environmental tobacco smoke includes a body of research on asthma and the relationship between parental smoking and preexistent disease in children. While only a few studies have been conducted thus far on children with, for example, cystic fibrosis (a genetic disorder whereby lung passages often become blocked by abnormally behaving mucus), there have been numerous studies that have examined asthmatic children and the presence of smokers in the home. The results of the studies have been variable and are subject to the influences of many different confounders such as socioeconomic status, genetic determinants, damp housing, and gas cooking in the home. It is not suprising, therefore, that researchers are inconsistent in their interpretation of the available data on exposure to ETS and childhood asthma. Following is a presentation of the major studies that have examined a possible association of ETS with asthma in children. Also included are the studies available on children with cystic fibrosis.

2023380000

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

RESULTS OF SELECTED STUDIES: COMPROMISED CHILDREN

Leeder, et al., 1976	Reported that episodes of asthma in the first five years of life showed an association with parental history of asthma-wheeze and that there is little relationship between asthma in the first five years of life and other family, social, or environmental factors.
Fergusson, et al., 1985	Reported that maternal smoking increased the risk of lower respiratory infections/symptoms during the child's first two years of life, and that after two years this association seemed to disappear. Also reported that there was no increased risk of asthma or asthma attacks attributable to maternal smoking.
Horwood, et al., 1985	Reported that there was no evidence to suggest that the structure, practices (including parental smoking), or the dynamics of the family played a significant role in the development of childhood asthma.
Murray, et al., 1986	Reported that maternal smoking aggravated symptoms in asthmatic children.

2023380001

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Anderson, et al., 1987	Reported that sex of child, mother's age at the child's birth, pneumonia, whooping cough, tonsillectomy, adenoidectomy, allergic rhinitis, eczema and periodic abdominal pain/vomiting attacks were associated with the development of childhood asthma.
Evans, et al., 1987	Reported that parental smoking increased the number of emergency room visits of children with asthma. The lack of an association between parental smoking and symptoms in asthmatic children caused the authors to question the mechanism whereby parental smoking would increase ER visits.
Toyoshima, et al., 1987	Reported that it was not clear whether parental smoking increased the incidence of asthmatic disease in children.
Kershaw, 1987	The authors conceded that the association observed with parental smoking may reflect a relationship of smoking behaviour to a number of other social factors such as medical care utilization and maternal stress.
Murray, et al., 1988	Reported that paternal smoking, including the number of cigarettes the father smoked at home, had no association with any test results. Maternal smoking in the "wet and cold" season was reported to increase the severity of the child's asthma. There was no assocation in the "warm and dry" season

2023380002

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

	and the severity of the child's asthma. The authors attribute this to increased ventilation in the "warm and dry" season.
Somerville, et al., 1988	Reported a positive association between parental smoking and asthma in girls and a non-significant negative relation between parental smoking and asthma in boys.
Oldigs, et al., 1990	Reported that in children with mild bronchial asthma one hour of passive smoke exposure did not cause airway obstruction or changes in bronchial responsiveness.
Sherman, et al., 1990	Neither bronchiolitis, eczema, croup, personal cigarette smoking, maternal smoking, paternal smoking, nor delivery complications bore an apparent relation to the development of childhood asthma.
Weitzman, et al., 1990	The authors concede that the estimate of children's exposure to cigarette smoke is "crude", based on parent reporting of smoking during pregnancy.
Rubin, 1990	Reported an association between parental smoking and the severity of cystic fibrosis in children. However, the authors conceded that it could not be ruled out that social, economic, or other factors determined both the smoking status of the household and the nutritional status of the children.

2023380003

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Gilljam, et al., 1990	Reported that there was no statistical difference in clinical status or pulmonary function between children with cystic fibrosis from smoking and nonsmoking families. For patients with higher levels of physical activity, parental smoking appeared to matter less.
Young, et al., 1991	Reported that parental smoking may contribute to a higher level of airway responsiveness early in the child's life. The authors conceded that they did not report the actual amount of parental smoking due to the inaccuracies of parental reporting.

2023380004

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023380005

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

PARENTAL SMOKING AND OTITIS MEDIA IN CHILDREN

2023380006

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

OTITIS MEDIA ("GLUE EAR")

In addition to claims that parental smoking affects the respiratory health of children, there are claims that exposure to parental smoking might increase the risk of otitis media (commonly known as "glue ear") in children. Otitis media is an inflammation of the inner ear that often leads to an accumulation of fluid in the inner ear canal. Otitis media often appears as a complication of various viral and bacterial infections, including measles. If left undetected, otitis media can lead to hearing loss and learning disabilities. Authors of studies examining this issue have not formulated a widely accepted mechanism for how ETS might increase the risk of otitis media in children. There are two theories that are proposed but have not been scientifically proven: 1) One theory is that ETS somehow chronically irritates the eustachian tube of the inner ear, leading to the inflammation; and 2) The second theory is that ETS potentially increases the risk of upper respiratory tract infections that spread to the inner ear. The results of the studies on this subject are variable and are subject to the same confounders that potentially bias the results of studies on other ETS related issues. While the science on this issue is controversial, the reported seriousness of otitis media makes investigators anxious to make recommendations for child safety. However, the studies on otitis media and parental smoking have not established a clear association.

2023380007

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

RESULTS OF SELECTED STUDIES ON OTITIS MEDIA

Said, et al., 1978	Reported that number of tonsillectomies/adenoidectomies were related to the amount of parental smoking in the home
Pukander, et al., 1985	Reported that parental smoking in the home increased the risk of acute otitis media and that breast-feeding seemed to have a protective effect
Kallail, et al., 1987	Reported that parental smoking was not associated with the occurrence of otitis media
Zielhuis, 1989	Reported that parental smoking was not related to an increased risk of otitis media
Strachan, 1990	Reported that parental smoking was an important determinant of middle-ear underpressure and effusion
Strachan, 1989	Reported that approximately one-third of the cases of middle ear effusion in their subjects were attributable to passive smoking
Taninio, et al., 1988	Reported that parental smoking was more prevalent among the subjects with recurrent otitis media
Kraemer et al, 1983	Reported that parental smoking, atopy, and catarrh posed the greatest risk to children of developing persistent middle-ear effusions when present together in the same child

2023380008

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Pukander, et al., 1990	Reported that maternal smoking increased the risk of acute otitis media in infants and especially of recurrent attacks
Vinther, et al., 1982	Reported that there were no effects of parental smoking on the frequency of otitis media in children
Moorhead, 1985	Reported that otitis media was found to be related to parental smoking in this general practice study
Black, 1985	Reported that parental smoking increased a child's risk of undergoing surgery for otitis media
Fleming, et al., 1987	Reported that full time day-care attendance increased the risk of ear infections (odds ratio = 3.8)

2023380009

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

ETS AND ADULT RESPIRATORY DISEASE/SYMPTOMS

2023380011

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

ADULT RESPIRATORY DISEASE

Several studies have examined respiratory disease and symptoms and their possible association with exposure to environmental tobacco smoke in adults. The studies that examined respiratory disease and symptoms in adults are contained in this section. For additional studies on adults, see the "compromised individuals" and "lung function" sections.

2023380012

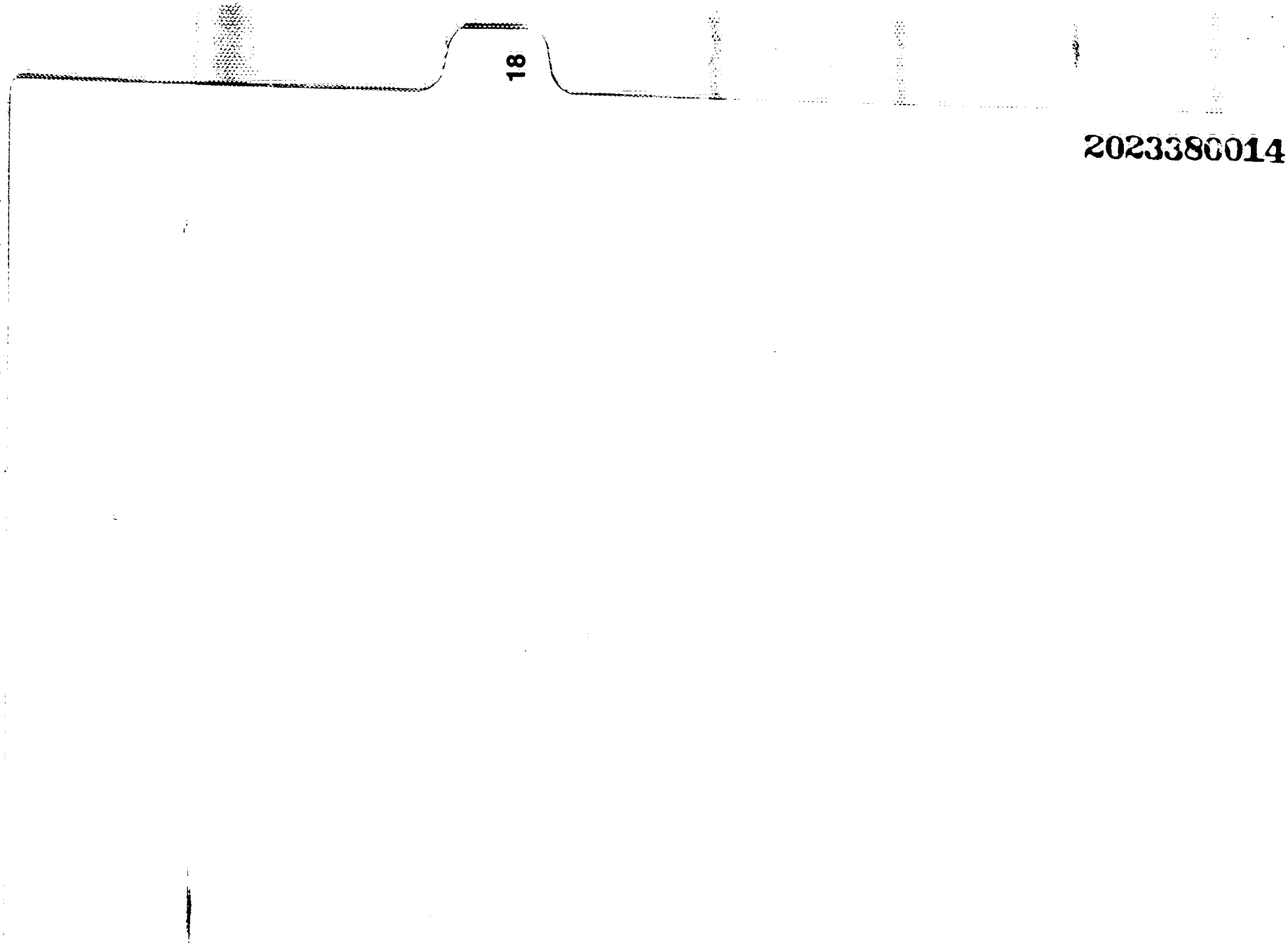
Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

RESULTS OF SELECTED STUDIES: ETS AND ADULT RESPIRATORY HEALTH

Lee, 1986	Passive smoking was not associated with an increased risk of chronic bronchitis in the nonsmoker.
Koo, et al., 1988	Reported an association between respiratory symptoms in the mothers and the same symptoms in their children. Indicates that cross-infection is an important confounder of studies on parental smoking and childhood respiratory health.
Hole, et al., 1989	Reported an association between passive smoking and adverse cardiorespiratory symptoms in adult nonsmokers. None of the associations, however, were significant.
Koo, et al., 1990	With the exception of smoking by the father and the children's NO2 levels, no association was found between smoking at home and NO2 levels.

2023380013

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000



Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

ETS AND ADULT LUNG FUNCTION

2023380015

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

LUNG FUNCTION IN ADULTS

The studies that have investigated lung function in adults and its possible relationship to environmental tobacco smoke exposure are presented in this section. To aid in the interpretation of this literature, definitions of the major lung function parameters are provided below.

Df: One of the most widely used measures of pulmonary function in adults and children is **forced vital capacity** and is represented in the literature as **FVC**. This term refers to the maximum volume of gas that a person can expire as forcefully and rapidly as possible from their lungs immediately following a maximal inspiration of air. When a person's ability to expire air forcefully and rapidly from their lungs (FVC) is compromised, this can possibly be an indication of chronic obstructive lung disease. Decreased FVC is common in restrictive diseases such as pulmonary fibrosis and in obstructive diseases such as emphysema and asthma.

Df: A second important measure of pulmonary function is the **forced expiratory volume in one second**, which is abbreviated as **FEV1** in the literature. The FEV1 measure is simply the amount of air that is expired in the first second of the FVC maneuver. As with FVC, this parameter is useful in the assessment of airway obstruction. The two parameters, FVC and FEV1, are often used in a ratio to determine the percentage of a person's FVC that is expired in the first second of the maneuver. A **FEV1/FVC ratio** lower than 65% to 70% is characteristic of obstructive lung disease. On the other hand, subjects with restrictive lung disease will often show a normal or exaggerated FEV1/FVC value.

Df: **Forced expiratory flow**, known as **FEF25%-75%**, is the average rate of flow of air during the middle half of an FEV maneuver. The FEF25%-75% is indicative of the status of the medium and small sized airways. Decreased values of FEF25%-75% are common in the early stages of obstructive lung disease. Low values of FEF25%-75% in combination with normal values of FVC and FEV1 are often indicative of early small airways abnormality. Reduced FEF25%-75% are sometimes seen in cases of severe restrictive disease as well.

All of these measures share a common problem: accurate assessment requires the full cooperation and maximal effort of the subjects under investigation. Accurate measures are sometimes

2023380016

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

therefore difficult to obtain. The studies are not consistent in the lung function parameters they measure, and there is also a lack of consistency among the results of the same function tests across studies. Following is a presentation of the major studies that have examined these lung function parameters in adults. The investigators who have found associations between impaired lung function and ETS exposure are often uncertain of the clinical meanings of the small decreases observed in their studies. Therefore, it is not suprising that no definitive conclusions have been reached regarding ETS exposure and its possible association with lung function in adults.

2023380017

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCE

Ruppel, Gregg. Manual of pulmonary function testing (Fourth edition). The C.V. Mosby Company, 1986, pp. 33-38.

2023380018

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

RESULTS OF SELECTED STUDIES: ETS AND ADULT LUNG FUNCTION

Bouhuys, et al., 1978	The authors reported no associations between smoking in the home and increased symptoms or lung function loss among nonsmokers living in the same households.
Shephard, et al., 1979	The authors raise the possibility that subjective reporting of symptoms could have been "suggested" by the odor of the cigarette smoke.
White, et al., 1980	This study has received numerous criticisms.
Comstock, et al., 1981	Passive smoking in the home was not associated with the prevalence of respiratory symptoms and was only "suggestively associated" with impaired ventilatory function.
Kauffmann, et al., 1983	Opposite trends in FEV1 and FEF25-75 were found in men passively exposed to tobacco smoke, and the differences observed in women were slight and not statistically significant.
Jones, et al., 1983	The use of cooking fuels was found to be associated with impaired ventilatory function in a group of nonsmoking women.
Kentner, et al., 1984	Passive inhalation of tobacco smoke at home or the workplace was found not to be associated with impaired lung function in healthy nonsmokers.
Lebowitz, et al., 1985	Reported no direct association between ETS and lung function parameters in adult nonsmokers.

2023380019

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Hosein, et al., 1986	The use of gas stoves was found to be associated with impaired lung function in women. It was reported that passive smoking in households where gas stoves were used appeared to have no effect on lung function values.
Masi, et al., 1988	The authors concede that their use of multiple tests of significance (involving both exposure and response measurements) are likely to have resulted in some associations achieving statistical significance by chance.
Kalandidi, et al., 1990	Assessment of exposure was based solely on the husband's smoking habit in terms of amount (daily), amount (total), and duration.

2023380020

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023380021

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

ETS AND COMPROMISED ADULTS

2023380022

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

COMPROMISED ADULTS

The literature on environmental tobacco smoke includes a body of research on asthmatic adults. Studies have been conducted in order to attempt to determine whether there is a relationship between passive exposure to ETS and the development of asthma or the exacerbation of existing asthma in adults. The studies are varied in their results, and accordingly, no definitive conclusions have been reached by investigators. Following are the studies that examine ETS and its possible relation to asthma in adults.

2023380023

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

COMMENTS ON SELECTED STUDIES: ETS AND COMPROMISED ADULTS

Stahle, et al., 1978	The authors suggest that tobacco smoke exposure might trigger asthma attacks by means of an allergic reaction.
Shephard, et al., 1979	Reported that asthmatic subjects did not appear to have an unusual sensitivity to tobacco smoke exposure.
Dahms, et al., 1981	Five of the ten subjects specifically reported sensitivity to tobacco smoke before their inclusion in this study.
Ing, et al., 1983	This study investigated only six subjects.
Romer, et al., 1983	The authors concede that the small subject population of this study indicates that the results must be taken with caution.
Knight, et al., 1985	Only six subjects were studied.
Wiedemann, et al., 1986	The authors report that passive smoking presents no acute respiratory risk to young asymptomatic asthmatic patients.
Stankus, et al., 1988	Only 21 subjects were included and all had complained of respiratory symptoms upon previous exposure to environmental tobacco smoke.
Bailey, et al., 1990	No relationship was observed between passive smoking and pulmonary function of asthmatic subjects.

2023380024

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023380025

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

CONFOUNDERS

2023380026

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

CONFOUNDERS

Studies on parental smoking and childhood respiratory disease rarely address confounding variables. Confounding variables are factors that can create a "false" association between two elements by being associated with one or both of them. For example, factor X (socioeconomic status) may be associated with both factor Y (parental smoking) and factor Z (childhood respiratory disease). When factor X is not controlled for in epidemiological studies of the possible association between factor Y and factor Z, a false association may appear between factors Y and Z. Therefore, it is vital that epidemiologists control for confounding variables when conducting studies such as those on parental smoking. The possible confounding variables associated with parental smoking and childhood respiratory disease can be grouped into four major categories: (1) household heating and cooking sources; (2) outdoor air pollution; (3) organic substances; and (4) demographic, medical and socioeconomic factors.

2023380027

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Household heating and cooking sources

Children living in households with gas stoves have been reported to have a greater history of respiratory illness before the age of two and small but significantly lower levels of FEV_1 and FVC corrected for height[1] (FEV1 and FVC are standard measurements of lung capacity and function). Similarly, exposure of children to gas cooking in the first two years of life has been associated with an increased risk of hospitalization for respiratory illness[2]. There are reported associations of gas stove use with daily peak flow in asthmatic, normal, and allergic subjects.[3]

Oxides of nitrogen (NOx) arising from the use of gas stoves for cooking were proposed to be related to a reported increase in cough, "colds going to the chest," and bronchitis in a study of 5,758 English and Scottish children aged six to eleven years[4]. A number of other confounders were controlled for in this study, including "age, social class, latitude, population density, family size, overcrowding, outdoor levels of smoke and sulphur dioxide and types of fuel used for heating." One group of researchers reported similar results for a five-year longitudinal study of 4827 boys and girls, ages five to ten years. This reported association was independent of age, sex, social class, number of cigarette smokers in the home, and latitude, and was only found in urban areas.[5]

2023380028

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Use of unvented kerosene heaters, which release nitrogen dioxide (NO_2) into the indoor environment, was associated with significantly more days of acute respiratory illness in exposed children[6]. In this study, there was no difference in the number of cigarettes smoked daily in the homes of exposed versus unexposed children. NO_2 exposure was also reported to be associated with a risk of reporting lower respiratory symptoms in children under the age of seven[7].

One study reported increased proportions of chest illnesses and hospitalizations for chest illness before age two in young children living in homes heated by wood-burning stoves. Medical histories, sociodemographic factors, or exposure to other pollutant sources did not account for the reported association[8].

In another report, hot water heating systems were reported to have a large effect on lung function in children, when compared to the use of forced air heating and air conditioning systems[9].

2023380029

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Speizer, F., et al., "Respiratory Disease Rates and Pulmonary Function in Children Associated with NO_2 Exposure," American Review of Respiratory Disease, 121(1): 3-10, 1980.

2. Ekwo, E.E., et al., "Relationship of Parental Smoking and Gas Cooking to Respiratory Disease in Children," Chest 84(6): 662-668.

3. Lebowitz, M.D., "The Effects of Environmental Tobacco Smoke Exposure and Gas Stoves on Daily Peak Flow Rates in Asthmatic and Non-Asthmatic Families," ETS - Environmental Tobacco Smoke: Report from a Workshop on Effects and Exposure Levels, eds., R. Rylander, et al., European Journal of Respiratory Diseases Suppl., 133(65): 90-97, 1984.

4. Melia, R.J.W., et al., "Association Between Gas Cooking and Respiratory Disease in Children," British Medical Journal, 149-152, 1977.

5. Melia, R.J.W., et al., "The Relation Between Respiratory Illness in Primary Schoolchildren and the Use of Gas for Cooking, I - Results From a National Survey," International Journal of Epidemiology, 8(4): 333-338, 1979.

2023380030

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

6. Berglund, B., et al., "Radon, Passive Smoking, Particulates and Housing Epidemiology," Indoor Air 2: 255-260, 1984.

7. Berwick, M., et al., "Lower Respiratory Symptoms in Children Exposed to Nitrogen Dioxide From Unvented Combustion Sources," Environment International 15: 369-373, 1989.

8. Osborne, J.S. and R.E. Honicky, "Health Effects of Heating With Wood: Chest Illness in Young Children and Indoor Heating with Woodburning Stoves," The Human Equation: Health and Comfort, ASHRAE/SOEH Indoor Air Quality '89, April 17-20, 1989, San Diego, CA.

9. Hosein, H.R., et al., "The Effect of Domestic Factors on Respiratory Symptoms and FEV_1," International Journal of Epidemiology 18(2): 390-396, 1987.

2023380031

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Outdoor air pollution

Outdoor air pollutants have been identified as a confounder in several studies. In one study, acute respiratory disease incidence was reported to be positively associated with higher ambient sulfate levels[1].

A group of researchers examined the importance of indoor and outdoor environmental factors (parental smoking, gas cooking, suspended particulates and sulfur dioxide) in the respiratory health of seven- to ten-year-old Canadian children. The researchers were unable to identify any effects of parental smoking or gas cooking because the prevalence of these variables was highest in an industrial area of high particulate pollution[2].

One researcher has reported a strong association between respiratory illness and particulate pollution in children living in a study site which experiences relatively high levels of particulate pollution[3].

A study comparing Israeli children living in a polluted industrial town versus those living in an unpolluted area reported that chronic respiratory symptoms and most pulmonary diseases were significantly more common among those children from the polluted town[4].

2023380032

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Harrington, W. and Krupnick, Alan J., "Short-Term Nitrogen Dioxide Exposure and Acute Respiratory Disease in Children," JAPCA 35: 1061-1087, 1985.

2. Kerigan, A., et al., "A Three-Year Cohort Study of the Role of Environmental Factors in the Respiratory Health of children in Hamilton, Ontario," American Review of Respiratory Disease, 133: 987-993, 1986.

3. Pope, C., "Respiratory Disease Associated with Community Air Pollution and a Steel Mill, Utah Valley," AJPH, 79(5): 623-628, 1989.

4. Goren, A.I. and S. Hellmann, "Prevalence of Respiratory Symptoms and Diseases in Schoolchildren Living in a Polluted and in a Low Polluted Area in Israel," Environmental Research 45: 28-37, 1987.

2023380033

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Organic substances

The relevance of home dampness in the etiology of respiratory symptoms in children is supported by current research which links dampness with the presence of molds, dust mites, fungi and other allergenic microbes.

In one study, odds ratios of 1.23 and 2.16 were reported for home dampness after adjustment for several factors, including maternal smoking, in a cohort study of 4,625 eight- to twelve-year-old children living in six United States cities[1]. The authors reported odds ratios for molds of 1.27 to 2.12 after adjustment for maternal smoking and several other factors.

Another study reported higher rates of respiratory symptoms and symptoms of infection and stress among children living in damp houses. The presence of "fungal mould" was also reported to be related to higher rates of respiratory symptoms, independent of smoking in the household[2]. In another study, the growth of fungi and molds in the home was directly related to respiratory symptoms and sensitization to common allergens in children[3].

Researchers have reported that children living in damp and moldy dwellings had a greater prevalence of respiratory symptoms and headache and fever than those living in dry homes. The authors reported a dose-response relationship with increasing

2023380034

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

numbers of symptoms reported in dwellings with higher severity of dampness and mold. All these differences persisted after controlling for possible confounding factors such as household income, cigarette smoking, unemployment, and overcrowding[4].

Atopic sensitization of children to house dust mites was reported to be related to home dampness[5].

2023380035

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Brunekreef, B., et al., "Home Dampness and Respiratory Morbidity in Children," American Review of Respiratory Diseases 140: 1363-1367, 1989.

2. Martin, C., et al., "Housing Conditions and Ill Health," British Medical Journal, 294: 1987.

3. Ownby, D. and J. McCullough, "Passive Exposure to Cigarette Smoke Does Not Increase Allergic Sensitization in Children," J Allergy Clin Immunol 82(4): 634-638, 1988.

4. Platt, S., et al., "Damp Housing, Mould Growth, and Symptomatic Health State," British Medical Journal, 298: 1673-1678, 1989.

5. Nordvall, S.L., et al., "Sensitization of Children in the Stockholm Area to House Dust Mites," Acta Paediatr Scan, 77(5): 716-720, 1988.

2023380036

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Demographic, medical and socioeconomic factors

Low socioeconomic status has been associated with an increased incidence of respiratory complications[1]. Factors related to lower socioeconomic status include: inadequate medical care, poor nutrition, poor outdoor air quality, increased parental coughing, higher gas stove usage, frequent change of address, and lower per capita living space. In a study of 1,050 European children aged eight and nine years, lifetime and current prevalence of wheeze were both significantly higher in children from low socioeconomic status[2].

Watkins, et al., (1986) reported high consultation rates for respiratory illness in children whose fathers were in manual occupations. This association was not explained by crowded home conditions or parental smoking[3]. Gardner, et al., (1984) reported significantly higher rates of lower respiratory disease in infants of low socioeconomic status[4].

Cross-infection also plays a role in the incidence of children's respiratory disease. For instance, in a 1988 paper, Koo, et al., reported that among Japanese and Hong Kong Chinese women, there was a highly significant correlation between the frequency of maternal respiratory illness and the frequency of respiratory illness in her children[5].

2023380037

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Cross-infection may be relevant to the reports of associations between day care attendance and respiratory illness. Anderson, et al., (1988) reported that care outside the home (day care) is an important factor for acquiring lower respiratory tract illness and infectious diseases in children under two years of age[6]. Gardner, et al., (1984) also noted significantly higher rates of lower respiratory disease among day care infants[4]. Fleming, et al., (1987) reported an increased risk for upper respiratory tract infection associated with day care attendance[7].

Familial characteristics and genetics may also act as confounders. For instance, in a 1982 publication, Lebowitz, et al., report that an observed relationship between children's pulmonary function and parental smoking disappeared when household aggregation of body mass was taken into account[8]. Another Lebowitz, et al., study (1984) also reported that there was "no remaining independent aggregation of pulmonary function measurements" after familial aggregation of body habitus was controlled for[9]. Genetic predisposition may play a role in respiratory illness and pulmonary function[10]; although cross-infection is also involved[11].

"Lifestyle" may also act as a confounder. A study in Copenhagen (Holma and Winding, 1977) examined 109 social, medical, housing, and hygiene factors on morbidity. The best predictors for health were "thriving" (satisfaction), followed by "housing standard" and "personal hygiene." The authors reported no effect

2023380038

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

of parental cigarette smoking on the respiratory health of young children[12]. A survey of 314 nonsmoking Hong Kong Chinese women and their children and 243 Japanese women and their children reported that chronic cough and sputum symptoms were at least 10 times more prevalent in Hong Kong[5]. This observation was attributed to occupational exposure to dust or fumes and household crowding among the Hong Kong mothers.

2023380039

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Kerigan, A., et al., "A Three-Year Cohort Study of the Role of Environmental Factors in the Respiratory Health of Children in Hamilton, Ontario," American Review of Respiratory Diseases, 133: 987-993, 1986.

2. Mitchell, E., et al., "Socioeconomic Status in Childhood Asthma," International Journal of Epidemiology, 18(4): 888-890, 1989.

3. Watkins, C.J., et al., "Patterns of Respiratory Illness in the First Year of Life," British Medical Journal, 293: 794-796, 1986.

4. Gardner, G., et al., "Effects of Social and Family Factors on Viral Respiratory Infection and Illness in the First Year of Life," Journal of Epidemiology and Community Health 38(1): 42-48, 1984.

5. Koo, L., et al., "A Comparison of the Prevalence of Respiratory Illness Among Nonsmoking Mothers and Their Children in Japan and Hong Kong," Respiratory Illnesses Among Japanese and Chinese Mothers and Their Children: 290-295, 1988.

2023380040

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

6. Anderson, L., et al., "Day Care Center Attendance and Hospitalization for Lower Respiratory Tract Illness," Pediatrics 82(3): 300-308, 1988.

7. Fleming, D.W., et al., "Childhood Upper Respiratory Tract infections: To What Degree Is Incidence Affected by Day-Care Attendance?" Pediatrics 79(1): 55-60, 1987.

8. Lebowitz, M., et al., "The Effect of Passive Smoking on Pulmonary Function in Children," Environment International, 8: 371-373, 1982.

9. Lebowitz, M., et al., "Family Aggregation of Pulmonary Function Measurements," American Review of Respiratory Diseases, 129: 8-11, 1984.

10. Colley, J.R.T., et al., "Influence of Passive Smoking and Parental Phlegm on Pneumonia and Bronchitis in Early Childhood," The Lancet II: 1031-1034, 1974.

11. Colley, J.R.T., "Respiratory Symptoms in Children and Parental Smoking and Phlegm Production," British Medical Journal 2: 201-204, 1974.

2023380041

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

12. Holma, B. and Winding, O., "Housing, Hygiene, and Health: A Study in Old Residential Areas in Copenhagen," Archives of Environmental Health 32(2): 86-93, 1977.

2023380042

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

PARENTAL SMOKING: CONFOUNDING VARIABLES

Access to medical care

Age of mother

Air pollution

Birth weight

Breast feeding

Cooking practices/type

Day care attendance

Diet

Family history of illness

Family size

Gender of child

Genetic determinants

Heating type

Home dampness

Hospital spread of illness

Household pets

Newborn illnesses

Nurture

Overcrowding

Parental education

Parental infections

Place of residence

Seasonal variation

Skin test reactivity (allergy)

Socioeconomic status

2023380043

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023380044

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

WORKPLACE SMOKING IS.

2023380045

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

I. HEALTH CLAIMS

- The claim that exposure to environmental tobacco smoke (ETS) in the workplace causes disease in nonsmokers is not justified on a scientific basis.

Exposure

- Measurements taken in offices, workplaces and public places indicate that the contribution of tobacco smoke to indoor air is minimal.[1] For example, typical nicotine measurements (which are particularly revealing because nicotine is unique to tobacco smoke) range from an exposure equivalent of 1/100 to 1/1000 of one filter cigarette per hour.[2] In other words, a nonsmoker would have to spend from 100 to 1000 hours in an office, restaurant or public place in order to be exposed to the nicotine equivalent of just one cigarette.

Lung Function

- A 1980 report[3] which concluded that nonsmokers exposed to tobacco smoke at work for 20 or more years had reduced function of the small airways compared to nonsmokers not so exposed still receives considerable attention, although it was heavily criticized for questionable data acquisition and analysis.[4] In contrast, a more recent study of 1,351 German office workers reportedly found "no evidence" that everyday exposure to

2023380046

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

tobacco smoke in the office or at home leads to an essential reduction of lung function in healthy adults.[5]

Lung Cancer

- Nine of the published studies on spousal smoking and lung cancer examined workplace exposure to ETS and the incidence of lung cancer in nonsmokers.[6] Not one of the studies provides adequate support for an association between ETS exposure in the workplace and lung cancer.

Allergy

- One of the most widespread beliefs, especially in the workplace setting, is that some nonsmokers are "allergic" to tobacco smoke. Scientific researchers, however, have not identified specific allergens in tobacco smoke.[7] Thus, while some individuals may react to the sight or smell of tobacco smoke, this does not mean that they are experiencing an "allergic" reaction to it.

2023380047

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Kirk, P., et al., "Environmental Tobacco Smoke in Indoor Air," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk, London, Selper Ltd.: 99-112, 1988.

Sterling, T., et al., "Environmental Tobacco Smoke and Indoor Air Quality in Modern Office Work Environment," J. of Occup. Med. 29(1): 57-62, 1987.

Proctor, C., et al., "Measurement of Environmental Tobacco Smoke in an Air-Conditioned Office Building," Present and Future of Indoor Air Quality, eds. C. Bieva et al., Amsterdam, Elsevier Science Publishers: 169-172, 1989.

Crawford, W., "Health Effects of Passive Smoking in the Workplace," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk, London, Selper Ltd.: 203-210, 1988.

Oldaker, G., et al., "Results from Surveys of Environmental Tobacco Smoke in Offices and Restaurants," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 99-104, 1990.

2. Badre, R., et al., "Pollution Atmospherique par la Fumee de Tabac (Atmospheric Pollution by Smoking)," Ann. Pharm. Fr. 36(9-10): 443-452, 1978. Translation.

Carson, J. and C. Erikson, "Results from Survey of Environmental Tobacco Smoke in Offices in Ottawa, Ontario," Environ. Technol. Letters 9: 501-508, 1988.

Hinds, W. and M. First, "Concentrations of Nicotine and Tobacco Smoke in Public Places," New Eng. J. of Med. 292(16): 844-845, 1975.

Jenkins, R., et al., "Development and Application of a Thermal Desorption-Based Method for the Determination of Nicotine in Indoor Environments," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk, London, Selper Ltd.: 557-566, 1988.

Muramatsu, M., et al., "Estimation of Personal Exposure to Ambient Nicotine in Daily Environment," Arch. Occup. Environ. Health 59: 545-550, 1987.

3. White, J. and H. Froeb, "Small-Airways Dysfunction in Nonsmokers Chronically Exposed to Tobacco Smoke," New Eng. J. of Med. 302(13): 720-723, 1980.

2023380048

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

4. Adlkofer, F., et al., "Small-Airways Dysfunction in Passive Smokers," New Eng. J. of Med. 303(7): 392, 1980.

Huber, G., "Small-Airways Dysfunction in Passive Smokers," New Eng. J. of Med. 303(7): 392, 1980.

Freedman, A., "Small-Airways Dysfunction in Passive Smokers," New Eng. J. of Med. 303(7): 393, 1980.

Aviado, D., "Small-Airways Dysfunction in Passive Smokers," New Eng. J. of Med. 303(7): 393, 1980.

Fountain, L.H., "White-Froeb Study Discredited by Scientists," U.S. Cong. Record, Ninety-Seventh Congress, Second Session, Washington, D.C., U.S. Government Printing Office, E5252-5254, December 16, 1982.

Lebowitz, M., "Influence of Passive Smoking on Pulmonary Function: A Survey," Preventive Medicine 13(6): 645-655, 1984.

5. Kentner, M., et al., "The Influence of Passive Smoking on Pulmonary Function - A Study of 1,351 Office Workers," Preventive Medicine 13(6): 656-669. 1984.

Kentner, M. and D. Weltle, "Passive Tobacco Smoke Inhalation and Lung Function in Adults," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk, London, Selper Ltd.: 232-241, 1988.

6. Kabat, G. and E. Wynder, "Lung Cancer in Nonsmokers," Cancer 53(5): 1214-1221, 1984.

Garfinkel, L., et al., "Involuntary Smoking and Lung Cancer: A Case-Control Study," JNCI 75(3): 463-469, 1985.

Shimizu, H., et al., "A Case-Control Study of Lung Cancer in Nonsmoking Women," Tohoku J. Exp. Med. 154: 389-97, 1988.

Koo, L., et al., "Measurements of Passive Smoking and Estimates of Lung Cancer Risk Among Non-Smoking Chinese Females," Int. J. Cancer 39: 162-169, 1987.

Wu, A., et al., "Smoking and Other Risk Factors for Lung Cancer in Women," JNCI 74(4): 747-751, 1985.

Lee, P., et al., "Relationship of Passive Smoking to Risk of Lung Cancer and Other Smoking-Associated Diseases," Brit. J. Cancer 54: 97-105, 1986.

2023380049

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

Svensson, C. et al., "Smoking and Passive Smoking in Relation to Lung Cancer in Women" Acta Oncologica 28: 623-629, 1989.

Wu-Williams, A., et al., "Lung Cancer Among Women in North-East China," Brit. J. of Cancer 62: 982-987, 1990.

Janerich, D. et al., "Lung Cancer and Exposure to Tobacco Smoke in the Household," New Eng. J. Med. 323(10): 632-636, 1990.

7. Lehrer, S., et al., "Tobacco Smoke Sensitivity: A Result of Allergy?," Ann Allergy 56: 1-10, 1986.

2023380050

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023380051

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

II. SICK BUILDING SYNDROME

Because it is visible and easily identified by its aroma, environmental tobacco smoke is often blamed for indoor air quality problems. Government and private studies of "sick buildings" in the United States, Canada and Europe report, however, that tobacco smoke may be involved in only two percent to five percent of the buildings investigated for complaints about air quality.[1] For example, from 1981 through 1987, one company studied indoor air quality in 223 different buildings, accounting for over 39 million square feet of property, and found that ETS was a significant concern in only 10, or 4%, of the buildings [Robertson, 1988]. In another SBS database, smoking was implicated as a major contributor to complaints in only 12 of 408 (<3%) of the buildings surveyed [Collett, 1989]. The National Institute for Occupational Safety and Health (NIOSH) investigated more than 200 "sick" buildings and found that tobacco smoke was the source of claimed discomfort in only 2% of the buildings investigated. Ventilation problems were associated with half the complaints; outdoor air was considered a bigger problem than ETS [Melius, 1984]. Other investigators concluded that bacterial and fungal contamination is a major source of indoor air problems [Collett, 1989; Robertson, 1988].

2023380052

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

- Inadequate ventilation exacerbates all indoor air quality problems. This suggests that even a total smoking ban is not likely to affect comfort problems in 95 to 98 percent of "sick buildings."[2]

- The majority of indoor air quality problems in "sick buildings" have been traced to inadequate fresh air and poor air filtration. Because the visibility of tobacco smoke may be an indicator of inadequate ventilation, the prohibition of smoking serves to mask the real reason for poor indoor air quality--lack of proper ventilation. In addition, concentrating on tobacco smoke ignores the fact that adequate ventilation should always be provided in any enclosed space, regardless of whether or not smoking is permitted.

2023380053

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Kirkbride, J., "Sick Building Syndrome: Causes and Effects," Health and Welfare Canada, Ottawa, Canada, 1985.

   Melius, J., et al., "Indoor Air Quality -- the NIOSH Experience," Ann. Am. Conf. Gov. Ind. Hydg. 10: 3-7, 1984.

   Robertson, G., "Source, Nature and Symptomology on Indoor Air Pollutants," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk, London, Selper Ltd.: 311-319, 1988.

   Collett, C. et al., "A Database of Problem Buildings: Learning by Past Mistakes," Present and Future of Indoor Air Quality, eds. C. Bieva et al.. Amsterdam, Elsevier Science Publishers: 413-419, 1989.

   Turner, S. and P. Binnie, "An Indoor Air Quality Survey of Twenty-Six Swiss Office Buildings," Indoor Air '90, Toronto, Canada: 27-32, 1990.

2. Sterling, T. and Kleven, S., "The Epidemiology of 'Sick Public Buildings'," Indoor Air Quality: Symposium, Buenos Aires, National Academy of Sciences of Buenos Aires: 79-107, 1989.

2023380054

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023380055

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

III. VENTILATION

- In 1981, The American Society of Heating, Refrigeration and Air-Conditioning Engineers (ASHRAE) issued a ventilation standard for public places (ASHRAE 62-1981).[1] The Standard established two levels of ventilation, one for areas in which smoking was permitted, and another substantially lower rate for areas where smoking was prohibited. The Standard was recently revised and reissued (ASHRAE 62-1989) with one prescribed ventilation rate, regardless of whether smoking was permitted or not. The decision to reject separate ventilation rates for smoking and nonsmoking areas was influenced by two areas of research: (1) The amount of ventilation required to remove indoor contaminants produced by humans, namely carbon dioxide and body odor, is also sufficient to remove typical amounts of ETS; and (2) ventilation rates for nonsmoking areas under ASHRAE 62-1981 were found to be inadequate and permitted airborne substances to increase, even in the absence of ETS.[2]

- Operating costs for increasing ventilation to meet specifications set forth in ASHRAE 62-1989 have been estimated at 3-5% over current annual energy expenditures for office buildings. Compliance with ASHRAE Standard 62-1989 will apparently have little effect on annual energy budgets.[3]

2023380056

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. American Society of Heating, Refrigeration and Air Conditioning Engineers, ASHRAE Standard 62-1989, "Ventilation for Acceptable Indoor Air Quality," Atlanta, ASHRAE Publications, 1989.

2. Burroughs, H., "ASHRAE: Addressing the Indoor Air Quality Challenge With Energy Conscious Design," eds. R. Perry and P. Kirk, Indoor and Ambient Air Quality, London, Selper Ltd.: 530-535, 1988.

3. Eto, J., "The HVAC Costs of Increased Fresh Air Ventilation Rates in Office Buildings Part 2," Indoor Air '90, Toronto, Indoor Air '90: 53-58, 1990.

2023380057

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023380058

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

IV. ACCOMMODATION

- Since the claim that exposure to tobacco smoke causes disease in nonsmokers is not scientifically justified,[1] the real issue regarding the "right" to smoke-free air is whether or not smoking should be prohibited because some people consider it to be an annoyance or nuisance.

Annoyance:

- Tobacco smoke may be an annoyance or nuisance to some people, but such complaints typically arise in poorly ventilated areas. Such complaints are most frequently associated with inadequate ventilation and to indoor substances other than ETS [See Section II: "Sick-Buildings"].

- Regulating a behavior such as smoking merely because some see it as an annoyance has undesirable consequences. Numerous individual behaviors could fall into the category of "annoyances," and to demand restrictions on all those potentially "annoying" behaviors is "to call for government regulation of everything."[2]

- Such regulations also reject the real possibility that people can work things out among themselves and may place a minority

2023380059

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

of individuals in the position to dictate what is "right" for everyone.

- The alternative to intrusive regulation is good manners, common courtesy and cooperation between smokers and nonsmokers. This alternative preserves the delicate balance of individual rights and allows for accommodation of everyone's desires.

2023380060

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Wu, J., "Summary and Concluding Remarks," Environmental Tobacco Smoke: Proceedings of the International Symposium at McGill University 1989, eds. D. Ecobichon and J. Wu, Lexington, Massachusetts, Lexington Books: 367-375, 1990.

Layard, M., "Environmental Tobacco Smoke and Cancer: The Epidemiologic Evidence," Environmental Tobacco Smoke: Proceedings 1989: 99-115, 1990.

Wexler, L., "Environmental Tobacco Smoke and Cardiovascular Disease: A Critique of the Epidemiological Literature and Recommendations for Future Research," Environmental Tobacco Smoke: Proceedings 1989: 139-152, 1990.

Witorsch, P., "Effects of ETS Exposure on Pulmonary Function and Respiratory Health in Adults," Environmental Tobacco Smoke: Proceedings 1989: 169-185, 1990.

Adlkofer, F., "Biological Effects After Exposure to ETS," Indoor Air Quality: Symposium, Buenos Aires, National Academy of Sciences of Buenos Aires: 61-76, 1989.

Gostomzyk, G., "Passive Smoking - Report on an International Symposium (23-25 October 1986)," Public Health 49: 212-215, 1987.

Wynder, E. and G. Kabat, "Health Care and Society: Environmental Tobacco Smoke and Lung Cancer," Present and Future of Indoor Air Quality, eds. C. Bieva et al., Amsterdam, Elsevier Science Publishers: 135-145, 1989.

2. Williams, W., "Cigarettes and Property Rights," Clearing the Air: Perspectives on Environmental Tobacco Smoke, ed. R. Tollison, Lexington, Massachusetts, D.C. Heath and Company: 39-52, 1988.

2023380061

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

The Separation Issue:

- The 1986 Report of the Surgeon General on ETS suggests that separation of smokers and nonsmokers is not effective in minimizing the nonsmoker's exposure to ETS. That claim was made without scientific support. Indeed, subsequent research indicates that simple separation of smokers and nonsmokers effectively minimizes ETS exposures for nonsmokers.[1-3]

- One recent study reported that the use of designated smoking areas reduced exposure to ETS by 95%.[1] Another study of a smoking-restricted office building reported that ambient nicotine in nonsmoking areas was virtually undetectable, suggesting that ETS had a negligible impact on the nonsmoking areas of the building.[2]

- Canadian researchers, in a series of reports, presented results on levels of ETS constituents in offices where smoking was regulated and unregulated. They reported no significant differences in average ETS constituent levels between nonsmoking offices that received recirculated air from designated smoking areas and nonsmoking offices that did not receive recirculated air.[3] They concluded:

> The results indicate that the provision of a designated, but not separately ventilated smoking area can effectively eliminate or—

2023380062

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

drastically reduce most components of environmental tobacco smoke from nonsmoking offices.

- A federally-sponsored study of ETS in aircraft cabins indicates that separation of smokers and nonsmokers is an effective means for reducing exposure to ETS.[4] The authors reported that many ETS constituent concentrations in nonsmoking sections were below the limit of detection. Similar results have been reported in other studies.[5]

2023380063

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

REFERENCES

1. Vaughan, W. and Hammond, K., "Impact of 'Designated Smoking Area' Policy on Nicotine Vapor and Particle Concentrations in a Modern Office Building," J. Air Waste Manage. Assoc. 40: 1012-1017, 1990.

2. Hedge, A., et al., "Building Ventilation and Smoking Policy Effects on Indoor Air Quality and Employee Comfort and Health," Indoor Air '90, Toronto, Canada, July 29-August 3: 739-744, 1990.

3. Sterling, T. and B. Mueller, "ETS in Offices and When Smoking Is Restricted to Designated but Not Separately Ventilated Areas," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 120-129, 1990.

   Sterling, T., "ETS Concentrations Under Different Conditions of Ventilation and Smoking Regulation," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk, London, Selper Ltd.: 89-98, 1988.

   Sterling, T. and Mueller, B., "Concentrations of Nicotine, RSP, CO and CO_2 in Nonsmoking Areas of Offices Ventilated by Air Recirculated from Smoking Designated Areas," Am. Ind. Hyg. Assoc. J. 49(9): 423-426, 1988.

   Sterling, T., et al., "Exposure to Environmental tobacco Smoke in the Non Industrial Workplace Under Different Conditions of Ventilation and Smoking Regulation," Present and Future of Indoor Air Quality, eds. C.J. Bieva, et al., Amsterdam, Elsevier Science Publishers: 111-118, 1989.

4. U.S. Department of Transportation, "Airliner Cabin Environment: Contaminant Measurements, Health Risks, and Mitigation Options: Final Report," eds. Nagda, N.L. et al., GEOMET Technologies, Inc., Report No. DOT-P-15-89-5, December 1989.

5. Oldaker, G. and Conrad, F., "Estimation of Effect of Environmental Tobacco Smoke on Air Quality Within Passenger Cabins of Commercial Aircraft," Environ. Sci. Technol. 21: 994-999, 1987.

   Malmfors, T., et al., "Air Quality in Passenger Cabins of DC-9 and MD-80 Aircraft," Environ. Technol. Letters 10: 613-628, 1989.

   O'Donnell, A., et al., "Air Quality, Ventilation, Temperature and Humidity in Aircraft," ASHRAE Journal: 42-46, 1991.

2023380064

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000

2023380065

Source: https://www.industrydocuments.ucsf.edu/docs/tlnx0000